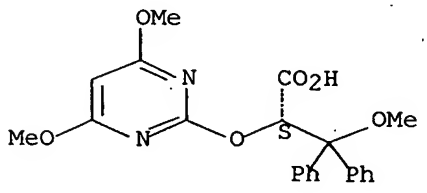
L11 ANSWER 1 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2006:213386 CAPLUS Full-text
TI Endothelin a receptor (eta) antagonists in combination with phosphodiesterase 5 inhibitors (pde5) and uses thereof
IN Keyser, Donald Jeffrey; Dixon, Richard
PA Encysive Pharmaceuticals, USA
SO PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2006026395	A1	20060309	WO 2005-US30342	20050826
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
PRAI US 2004-604462P	P	20040826		
US 2005-211099	A	20050825		

AB The invention relates generally to combination therapies comprising an endothelin A receptor (ETA) antagonist and a phosphodiesterase 5 (PDE5) inhibitor, pharmaceutical compns. comprising ETA antagonist and PDE5 inhibitor and methods of treating various disorders comprising administering an ETA antagonist and a PDE5 inhibitor. In particular, the combination therapies and pharmaceutical compns. are useful for the treatment and/or prevention of cardiac disorders such as pulmonary arterial hypertension (PAH). No significant pharmacokinetic interactions between sitaxsentan and sildenafil were demonstrated in healthy volunteers.

IT INDEXING IN PROGRESS
IT **171714-84-4**, LU135252 **177036-94-1**, LU208075
221176-51-8
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ETA antagonist and PDE5 inhibitor combinations for treating vascular disorders)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

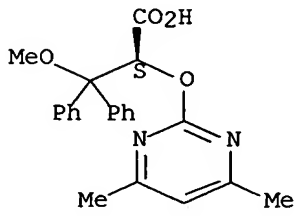
Absolute stereochemistry.



RN 177036-94-1 CAPLUS

CN Benzenepropanoic acid, α-[(4,6-dimethyl-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

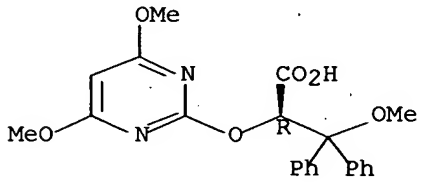
Absolute stereochemistry.



RN 221176-51-8 CAPLUS

CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 2 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2006:54076 CAPLUS Full-text
DN 144:135270
TI Enoximone formulations and their use in the treatment of PDE III-mediated diseases
IN Gerber, Michael; Gorczynski, Rick; Bristow, Mike
PA Myogen, Inc., USA
SO PCT Int. Appl., 71 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2006007213	A1	20060119	WO 2005-US18693	20050526

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

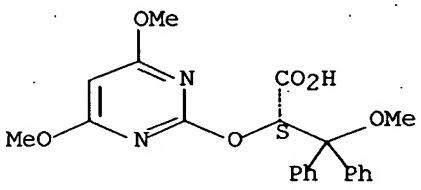
PRAI US 2004-582194P P 20040623

AB The present invention provides oral, parenteral and topical formulations of enoximone for use in treatment of disease states in which inhibition of phosphodiesterase III (PDE-III) may be beneficial. For example, enoximone administered to spontaneously hypertensive rats decreased the blood pressure by 42% at a 45 and 60 min time point at the dose of 100 mg/kg and 30 mg/kg. Enoximone also produced dose dependent increases in coronary blood flow (12 ± 2% at 0.1 mg/kg and 41 ± 6% at 1 mg/kg) in dogs.

IT **171714-84-4**, Darusentan **177036-94-1**, Ambrisentan
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(enoximone formulations and their use in treatment of PDE III-mediated diseases)

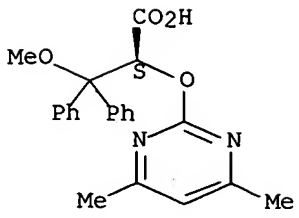
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 177036-94-1 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethyl-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

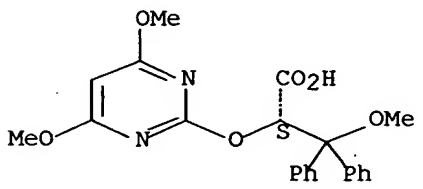
Absolute stereochemistry.



RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 3 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2005:1169524 CAPLUS Full-text
DN 144:210315
TI The endothelin/nitric oxide balance determines small-for-size liver injury after reduced-size rat liver transplantation
AU Palmes, Daniel; Minin, Evgeny; Budny, Tymoteusz; Uhlmann, Dirk; Armann, Barbara; Stratmann, Udo; Herbst, Hermann; Spiegel, Hans-Ullrich
CS Surgical Research, Department of General Surgery, Muenster University Hospital, Muenster, 48149, Germany
SO Virchows Archiv (2005), 447(4), 731-741
CODEN: VARCEM; ISSN: 0945-6317
PB Springer
DT Journal
LA English
AB Small-for-size (SFS) liver graft injury is probably related to microcirculatory disorders due to an imbalance of vasoconstricting, e.g. endothelin (ET)-1, and vasorelaxing mediators, e.g. nitric oxide (NO). We studied the role of ET-1/NO balance and the effect of an endothelin A receptor (ETAR) antagonist on SFS injury after liver resection and reduced-size liver transplantation (RSLT). One hundred twenty-six Lewis rats were divided into five groups: (I) 70% liver resection, (II) 70% liver resection treated with the ETAR antagonist LU 135252 (1 mg/kg b.w. i.v.), (III) RSLT (30% residual liver volume), (IV) RSLT treated with the ETAR antagonist, (V) sham operation. Liver microcirculation was measured by intravital microscopy. ET-1, ETAR, endothelial NO-synthase (eNOS), activation of Kupffer cells (KCs) and parenchymal injury were studied by immunohistol. Survival and liver function were followed up to 14 days. RSLT led to increased ET-1, ETAR and decreased eNOS protein expression, accompanied by activation of KC, reduced perfusion rate, vasoconstriction and elevated sinusoidal blood flow, as well as hepatocellular damage, impaired liver function and impaired survival. ETAR blockade (groups II + IV) improved the ET-1/NO balance, attenuated microcirculatory disorders and improved hepatocellular apoptosis and liver function. Microcirculatory disorders related to an ET-1/NO imbalance may contribute to SFS liver injury. Maintenance of ET-1/NO balance by blocking ETAR reduces SFS injury by protecting liver microcirculation, thus reducing hepatocellular damage.
IT **171714-84-4**, LU 135252
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(ETAR antagonist LU 135252 attenuated microcirculatory disorders and their morphol. sequelae by correcting ET-1/NO balance, preventing small-for-size liver injury in rat after reduced-size liver transplantation and liver resection)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

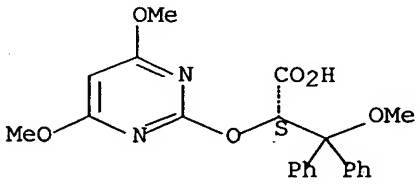
Absolute stereochemistry.



RE.CNT 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 4 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2005:1124511 CAPLUS Full-text
DN 143:379467
TI Effects of chronic endothelin ETA receptor blockade on blood pressure and vascular formation of cyclic guanosine-3',5'-monophosphate in spontaneously hypertensive rats
AU Kirchengast, Michael; Witte, Klaus; Stolpe, Kerstin; Schilling, Lothar; Nedvetsky, Pavel I.; Schmidt, Harald H. H. W.; Lemmer, Bjoern
CS Institute of Pharmacology and Toxicology, Ruprecht Karls University Heidelberg, Mannheim, Germany
SO Arzneimittel Forschung (2005), 55(9), 498-504
CODEN: ARZNAD; ISSN: 0004-4172
PB Editio Cantor Verlag
DT Journal
LA English
AB Endothelin (ET) mediates vasoconstriction in intact arterial blood vessels with functional endothelium via stimulation of ETA receptors, while ETB receptor stimulation leads to vasodilation via nitric oxide (NO) release and formation of cyclic guanosine-3',5'-monophosphate (cGMP). In spontaneously hypertensive rats (SHR) the cGMP-forming NO-receptor guanylyl cyclase (sGC) is downregulated. It is unclear whether ET contributes to the hypertensive phenotype of SHR, and whether this involves the disturbed cGMP signaling. The selective ETA receptor antagonist darusentan, given orally via drinking water (10 mg kg-1 d-1) for 12 wk, significantly lowered systolic blood pressure of SHR as determined by radiotelemetry. Neither impaired endothelium-dependent relaxation to acetylcholine was restored nor sGC expression and activity affected when compared to control SHR. While these findings show a role for ETA receptors in blood pressure regulation in genetically elevated blood pressure, downregulation of sGC expression and cGMP-mediated vasorelaxant response in SHR were shown to be independent of ETA receptors. The findings suggest distinct mechanisms of gene expression affecting ET and cGMP mediated vasomotor functions.
IT **171714-84-4**, Darusentan
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(effects of chronic endothelin ETA receptor blockade on blood pressure and vascular formation of cGMP in spontaneously hypertensive rats)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

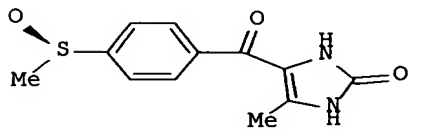


RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 5 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2005:1075630 CAPLUS Full-text
DN 143:353386
TI (R)-enoximone sulfoxide and its use in the treatment of PDE-III mediated diseases
IN Bristow, Michael R.; Gerber, Michael J.; Gorczynski, Richard J.
PA Myogen, Inc., USA
SO PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2005092333	A1	20051006	WO 2005-US9632	20050322
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2006030611	A1	20060209	US 2005-87076	20050322
PRAI	US 2004-555182P	P	20040322		

GI



I

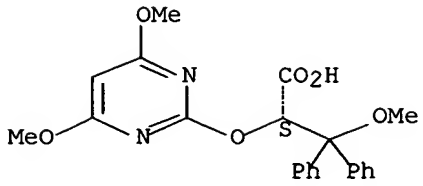
AB The present invention provides the (R)-(+)-enoximone sulfoxide (I) enantiomer, as well as pharmaceutical formulations of the purified (R)-(+)-sulfoxide enantiomer. Also provided are methods of treating diseases in which inhibition of PDE-III may be beneficial. I had had a greated contractility than the S enantiomer in explanted human hearts.

IT **171714-84-4**, Darusentan **177036-94-1**, Ambrisentan
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
((R)-enoximone sulfoxide and its use in the treatment of PDE-III mediated diseases)

RN 171714-84-4 CAPLUS

CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

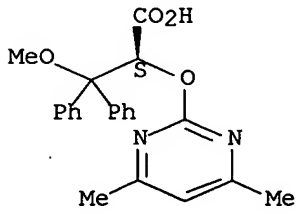
Absolute stereochemistry.



RN 177036-94-1 CAPLUS

CN Benzenepropanoic acid, α-[(4,6-dimethyl-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

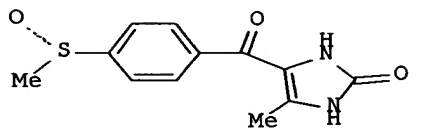


RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 6 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2005:1075629 CAPLUS Full-text
DN 143:353385
TI (S)-enoximone sulfoxide and its use in the treatment of PDE-III mediated diseases
IN Bristow, Michael R.; Gerber, Michael J.; Gorczynski, Richard J.
PA Myogen, Inc., USA
SO PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2005092332	A1	20051006	WO 2005-US9517	20050322
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2006025463	A1	20060202	US 2005-87059	20050322
PRAI US 2004-555261P	P	20040322		

GI



I

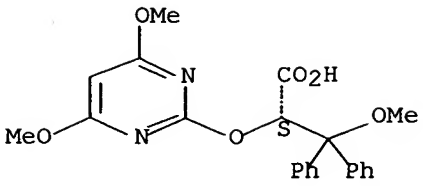
AB The present invention provides the (S)-(+)-enoximone sulfoxide (I) enantiomer, as well as pharmaceutical formulations of the purified (S)-(+)-sulfoxide enantiomer. Also provided are methods of treating diseases in which inhibition of PDE-III may be beneficial. I had had a greated contractility than the R enantiomer in explanted human hearts.

IT **171714-84-4**, Darusentan **177036-94-1**, Ambrisentan
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
((S)-enoximone sulfoxide and its use in the treatment of PDE-III mediated diseases)

RN 171714-84-4 CAPLUS

CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

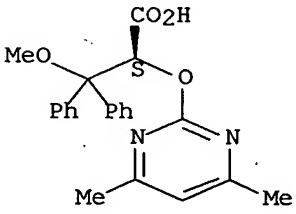
Absolute stereochemistry.



RN 177036-94-1 CAPLUS

CN Benzenepropanoic acid, α-[(4,6-dimethyl-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

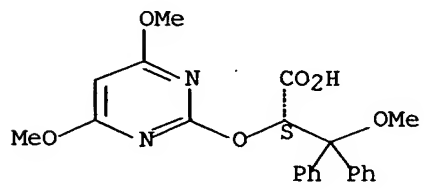
Absolute stereochemistry.



RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 7 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2005:972396 CAPLUS Full-text
DN 144:100647
TI Regression of Medial Elastocalcinosis in Rat Aorta
AU Essalihi, Rachida; Dao, Huy Hao; Gilbert, Liz-Ann; Bouvet, Celine; Semerjian, Yves; McKee, Marc D.; Moreau, Pierre
CS Faculty of Pharmacy, Universite de Montreal, Montreal, QC, Can.
SO Circulation (2005), 112(11), 1628-1635
CODEN: CIRCAZ; ISSN: 0009-7322
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB Background: We sought to determine whether carbonic anhydrase (CA), which plays an important role in bone resorption, contributes to vascular mineral loss induced by an endothelin receptor antagonist. Methods and Results: Wistar rats were compared with rats receiving warfarin and vitamin K1 (WVK) for 8 wk alone or in association with the endothelin receptor antagonist darusentan (30 mg/kg per day), the CA inhibitor acetazolamide (100 mg/kg per day), or both for the last 4 wk. Rats were also treated with WVK for 5 or 6 wk, and darusentan was added for the last week or last 2 wk of treatment, resp. Treatment with WVK produced medial elastocalcinosis in the aorta and carotid arteries. Immunohistochem. revealed that CA II was already abundant in the adventitia and in calcified areas of aortic sections from WVK-treated rats. Darusentan did not significantly modify its abundance or distribution. In contrast, CA IV immunostaining, which was weak in WVK-treated rats, became apparent after 1 wk of darusentan treatment and declined toward basal levels thereafter. These findings were confirmed by a parallel increase in CA IV protein abundance and activity in the aorta. The mineral loss induced by darusentan was blunted by acetazolamide treatment, confirming the functional relevance of the biochem. findings. Moreover, CA IV immunostaining was enhanced much later in the carotids, where darusentan did not cause regression of elastocalcinosis. Conclusions: Vascular mineral loss induced by the blockade of endothelin receptors seems dependent on the activation of membrane-bound CA IV, suggesting that mineral loss may proceed via local changes in pH similar to that seen in bone resorption.
IT **171714-84-4**, Darusentan
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); BIOL (Biological study)
(mineral loss induced by endothelin receptor antagonist darusentan was blunted by acetazolamide treatment suggested mineral loss seems to dependent on activation of membrane-bound CA IV in rat model for medial elastocalcinosis)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

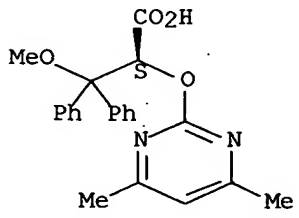
Absolute stereochemistry.



RE.CNT 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 8 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2005:951713 CAPLUS Full-text
DN 143:451884
TI Drug treatment of pulmonary arterial hypertension: current and future agents
AU Hoeper, Marius M.
CS Department of Respiratory Medicine, Hannover Medical School, Hannover, Germany
SO Drugs (2005), 65(10), 1337-1354
CODEN: DRUGAY; ISSN: 0012-6667
PB Adis International Ltd.
DT Journal; General Review
LA English
AB A review. During the last decade we have witnessed substantial improvements in the therapeutic options for pulmonary arterial hypertension (PAH), including true innovations targeting some of the mechanisms involved in the pathogenesis of this devastating disease. I.v. epoprostenol was the first drug to improve symptoms and survival of patients with PAH. Novel prostanoids, including s.c. treprostinil and inhaled iloprost, also have beneficial effects in many patients, although their long-term efficacy is less well known. Among the newer treatments for PAH, endothelin receptor antagonists and phosphodiesterase type 5 (PDE5) inhibitors have reshaped clin. practice. The endothelin receptor antagonist bosentan has been approved in many parts of the world and most current guidelines recommend this drug as first-line treatment for patients with PAH in functional class III. Novel endothelin receptor antagonists such as sitaxsentan sodium and ambrisentan are currently being investigated. The PDE5 sildenafil is also being intensively studied in patients with pulmonary hypertension, and most of the available data look promising, although approval for PAH is still pending. Other PDE5 inhibitors have not yet undergone extensive study in PAH. The increasing insight into the pathogenesis of PAH opens several new therapeutic opportunities, which include vasoactive intestinal peptide, selective serotonin reuptake inhibitors, adrenomedullin and HMG-CoA reductase inhibitors (statins). However, PAH is a complex disorder and targeting a single pathway can not be expected to be uniformly successful. Thus, combining substances with different modes of action is expected to improve symptoms, hemodynamics and survival in PAH patients, although combination therapy has yet to undergo the scrutiny of large randomised clin. trials.
IT **177036-94-1**, Ambrisentan
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ambrisentan may be used for treatment of pulmonary arterial hypertension patient)
RN 177036-94-1 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethyl-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 153 THERE ARE 153 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 9 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2005:735096 CAPLUS Full-text
DN 143:199988
TI Use of endothelin antagonists to prevent restenosis
IN Carlyle, Wenda
PA USA
SO U.S. Pat. Appl. Publ., 16 pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2005175667	A1	20050811	US 2005-54009	20050208
WO 2005077347	A1	20050825	WO 2005-US4315	20050210

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI US 2004-543252P	P	20040210	
US 2005-54009	A	20050208	

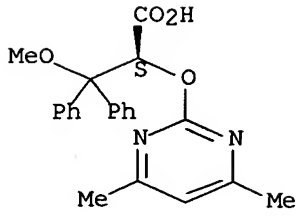
AB Provided are devices and methods for treating or preventing smooth muscle cell proliferation caused by endothelin-mediated conditions. In particular, a medical device comprising a structure which is implantable within a body lumen and means on or within the structure for releasing an endothelin (A) receptor antagonist at a rate effective to inhibit smooth muscle cell proliferation. The device can be, for example, an expansible stent or a graft, and the means can include a matrix coating, wherein the endothelin (A) receptor antagonist can be dispersed within the coating or disposed directly on the structure and under the matrix. The methods and devices of this invention can be used to decrease the incidence of restenosis as well as other thromboembolic complications resulting from implantation of medical devices. For example, Nitinol stents were cleaned in an ultrasonic bath with iso-Pr alc., dried and plasma cleaned in a plasma chamber. The cleaned stents were dip coated with an ethylene-vinyl alc. copolymer (EVOH) solution containing DMSO and Ambrisentan, and then passed over a hot plate, for about 3-5 s, with a temperature setting of about 60°. The coated stents were heated for 6 h in an air box and then placed in an oven at 60° under vacuum condition for 24 h to complete evaporation of the solvent.

IT **177036-94-1**, Ambrisentan
RL: DEV (Device component use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(implantable devices comprising endothelin receptor antagonists for prevention of vascular smooth muscle cell proliferation)

RN 177036-94-1 CAPLUS

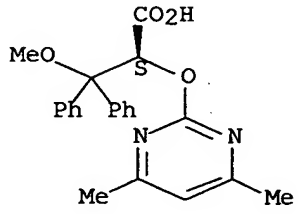
CN Benzenepropanoic acid, α-[(4,6-dimethyl-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.


CO2H
MeO
S
O
Ph
Ph
N
N
Me
Me

L11 ANSWER 10 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2005:699533 CAPLUS Full-text
DN 143:378869
TI Ambrisentan for pulmonary arterial hypertension
AU Rubin, Lewis J.; Dufton, Christopher; Gerber, Michael J.
CS Univ. California, LaJolla, CA, 9300, USA
SO Future Cardiology (2005), 1(4), 425-432
CODEN: FCUAAZ; ISSN: 1479-6678
PB Future Medicine Ltd.
DT Journal; General Review
LA English
AB A review. Endothelin receptor antagonists (ERAs) are an important class of agents used for the treatment of pulmonary arterial hypertension (PAH). Ambrisentan is an oral, once-daily, endothelin type-A receptor (ETA)-selective, propanoic acid class ERA under clin. investigation for the treatment of PAH. In a Phase II study, ambrisentan improved 6-min walk distance, Borg dyspnea index, World Health Organization Functional Class, and hemodynamics. Ambrisentan was well tolerated and adverse events were not dose related, including a low incidence and severity of liver function test abnormalities. There are no relevant interactions between ambrisentan and cytochrome P 450 isoenzymes (metabolism, induction or inhibition) that might alter the activity of P 450-metabolized drugs. Potential benefits of ambrisentan include oral, once-daily dosing, ETA-receptor selectivity, and the decreased risks of liver toxicity and adverse drug-drug interactions compared with other ERAs.
IT **177036-94-1**, Ambrisentan
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(endothelin receptor antagonist ambrisentan used against PAH may provide addnl. clin. benefits including oral, once-daily dosing, ETA-selectivity and decreased risk of liver toxicity and adverse drug-drug interaction)
RN 177036-94-1 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethyl-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

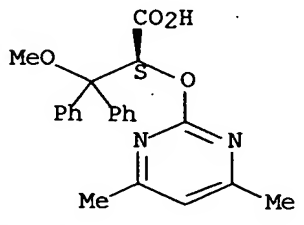
Absolute stereochemistry.



RE.CNT 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 11 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2005:686407 CAPLUS Full-text
DN 143:432302
TI Ambrisentan therapy for pulmonary arterial hypertension
AU Galie, Nazzareno; Badesch, David; Oudiz, Ronald; Simonneau, Gerald; McGoon, Michael D.; Keogh, Anne M.; Frost, Adaani E.; Zwicke, Diane; Naeije, Robert; Shapiro, Shelley; Olschewski, Horst; Rubin, Lewis J.
CS University of Bologna, Bologna, Italy
SO Journal of the American College of Cardiology (2005), 46(3), 529-535
CODEN: JACCDI; ISSN: 0735-1097
PB Elsevier Inc.
DT Journal
LA English
AB The purpose of this study was to examine the efficacy and safety of four doses of ambrisentan, an oral endothelin type A receptor-selective antagonist, in patients with pulmonary arterial hypertension (PAH). Pulmonary arterial hypertension is a life-threatening and progressive disease with limited treatment options. Endothelin is a vasoconstrictor and smooth muscle cell mitogen that plays a critical role in the pathogenesis and progression of PAH. In this double-blind, dose-ranging study, 64 patients with idiopathic PAH or PAH associated with collagen vascular disease, anorexigen use, or human immunodeficiency virus infection were randomized to receive 1, 2.5, 5, or 10 mg of ambrisentan once daily for 12 wk followed by 12 wk of open-label ambrisentan. The primary end point was an improvement from baseline in 6-min walk distance (6MWD); secondary end points included Borg dyspnea index, World Health Organization (WHO) functional class, a subject global assessment, and cardiopulmonary hemodynamics. At 12 wk, ambrisentan increased 6MWD (+36.1 m, $p < 0.0001$) with similar and statistically significant increases for each dose group (range, +33.9 to +38.1 m). Improvements were also observed in Borg dyspnea index, WHO functional class, subject global assessment, mean pulmonary arterial pressure (-5.2 mm Hg, $p < 0.0001$), and cardiac index (+0.33 l/min/m2, $p < 0.0008$). Adverse events were mild and unrelated to dose, including the incidence of elevated serum aminotransferase concns. >3 times the upper limit of normal (3.1%). Ambrisentan appears to improve exercise capacity, symptoms, and hemodynamics in patients with PAH. The incidence and severity of liver enzyme abnormalities appear to be low.
IT **177036-94-1**, Ambrisentan
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ambrisentan improved exercise capacity, quality of life, cardiac index and decreased pulmonary artery pressure, pulmonary vascular resistance with mild adverse effects in pulmonary arterial hypertension patient)
RN 177036-94-1 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethyl-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

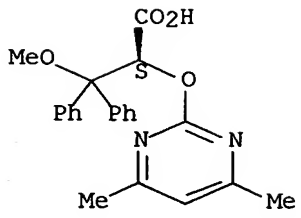
Absolute stereochemistry.



RE.CNT 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 12 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2005:625785 CAPLUS Full-text
DN 144:49361
TI Effects of ETA Receptor Antagonism on Proinflammatory Gene Expression and Microcirculation Following Hepatic Ischemia/Reperfusion
AU Uhlmann, Dirk; Gaebel, Gabor; Ludwig, Stefan; Armann, Barbara; Hess, Jochen; Pietsch, Uta-Carolin; Tannapfel, Andrea; Fiedler, Martin; Kratzsch, Juergen; Hass, Johann; Witzigmann, Helmut
CS Department of Abdominal, Transplantation and Vascular Surgery, Leipzig, Germany
SO Microcirculation (Philadelphia, PA, United States) (2005), 12(5), 405-419
CODEN: MROCER; ISSN: 1073-9688
PB Taylor & Francis, Inc.
DT Journal
LA English
AB Background: The objective of this study was to investigate the effect of a specific endothelinA receptor antagonist (ETA-RA) on mRNA expression of genes encoding vasoactive mediators and proinflammatory cytokines and on the microhemodynamics (assessed by measurement of laser Doppler flow and tissue blood gases) following complete vascular exclusion of the porcine liver. Study design: Sixteen adult German landrace pigs were subjected to 120 min of warm hepatic ischemia by total vascular exclusion. To avoid portal congestion, a passive porto-femoro/jugular bypass was implanted. The animals were divided into 2 groups: the control group received saline solution and the therapy group was given the selective ETA-RA BSF 208075. Hepatic microcirculation was evaluated by pO2 and pCO2 measurement with the Paratrend sensor and by laser Doppler flow measurement. Liver tissue samples were collected 1 h after reperfusion and quant. mRNA expression for prepro-ET-1, pro-IL-1β, pro-IL-6, pro-TNF-α, eNOS was analyzed using the TaqMan system. Addnl., immunohistochem. anal. using a semiquant. score for ET-1 was performed. Postischemic liver damage was monitored by measurement of liver enzymes and assessed by histol. anal. using a semiquant. scoring classification. Results: Partial oxygen pressure in the hepatic tissue and laser Doppler flow were significantly improved in the therapy group. One hour after reperfusion, quant. RT-PCR revealed significantly lower expression of prepro-ET-1, eNOS, pro-TNF-α, and pro-IL-6 in the therapy group compared to controls. Immunohistochem. anal. demonstrated significantly reduced ET-1 immunostaining after therapy. Furthermore, blockade of ETA receptors prevents tissue damage. Conclusions: Treatment with the selective ETA-RA BSF 208075 has protective effects on microcirculation after 120 min liver ischemia and reperfusion. The authors were able to show that ETA-RA not only affects the expression of vasoactive genes, but also decreases gene expression of proinflammatory cytokines such as TNF-α and IL-6.
IT **177036-94-1**, BSF 208075
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(selective endothelinA receptor antagonist BSF 208075 had protective effects on microcirculation, decreased gene expression of prepro-ET-1, eNOS, pro-TNF-α, pro-IL-6 following hepatic ischemia/reperfusion injury in pig model)
RN 177036-94-1 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethyl-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

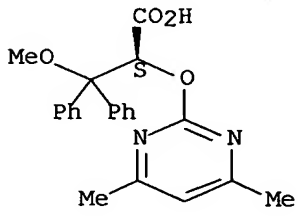
L11 ANSWER 13 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2005:474950 CAPLUS Full-text
DN 143:1287
TI Use of antiproliferative agents in the treatment and prevention of pulmonary proliferative vascular diseases
IN Kao, Peter N.; Pearl, Ronald G.; Nishimura, Toshihiko; Faul, John L.
PA USA
SO U.S. Pat. Appl. Publ., 30 pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2005119330	A1	20050602	US 2004-801729	20040315
PRAI US 2003-455470P	P	20030317		

AB Methods of treating lung proliferative vascular disorders by administering an antiproliferative agent are provided. A preferred antiproliferative agent is a HMG-CoA reductase inhibitor, preferably simvastatin. Vascular occlusion in the pulmonary arteries of the patient is reduced as a result of the treatment through a reduction in neointimal hyperplasia and medial hypertrophy, and the restoration of normal endothelial cell function. The treatment also results in a reversal of right side cardiac hypertrophy. Lung proliferative vascular disorders that can be treated include primary pulmonary hypertension, secondary pulmonary hypertension, Eisenmenger's syndrome, chronic thromboembolic disease, pulmonary fibrosis, obliterative bronchiolitis, or lymphangioleiomyomatosis. Dosages and pharmaceutical formulations are provided.

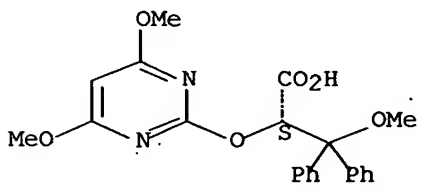
IT **177036-94-1**, Ambrisentan
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use of antiproliferative agents in treatment and prevention of pulmonary proliferative vascular diseases)
RN 177036-94-1 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethyl-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



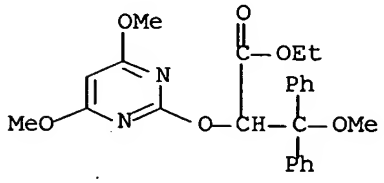
L11 ANSWER 14 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2005:391929 CAPLUS Full-text
DN 143:206041
TI Endothelin A antagonist LU-135252 and trandolapril in the treatment of the Cohen-Rosenthal diabetic hypertensive rat
AU Hofman, Cipy; Gabai, Efraim; Peleg, Edna; Munter, Klaus; Rosenthal, Talma
CS The Hypertension Unit, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv-Jaffa, Israel
SO Blood Pressure (2005), 14(2), 114-119
CODEN: BLPREG; ISSN: 0803-7051
PB Taylor & Francis Ltd.
DT Journal
LA English
AB Background: Hypertension and non-insulin-dependent diabetes mellitus (NIDDM) often occur simultaneously and the combination requires vigorous control of hypertension. This can generally be achieved by a combination of antihypertensive drugs. The present study examines the antihypertensive and possible hypoglycemic effects of combined therapy with endothelin A (ETA) receptor antagonist LU-135252 and angiotensin-converting enzyme (ACE) inhibitor trandolapril in male Cohen-Rosenthal Diabetic Hypertensive (CRDH) rats. Methods: Rats were divided into four groups as follows: group I served as control; group II - LU-135252 30 mg/kg/day; group III - trandolapril 0.1 mg/kg/day and group IV - both LU-135252 30 mg/kg/day and trandolapril 0.1 mg/kg/day. Systolic blood pressure (SBP) and plasma glucose levels were evaluated at the beginning of the experiment and after 2, 4 and 6 wk. Results: SBP decreased significantly in all treated groups after 2, 4 and 6 wk of treatment compared to baseline. Maximum decrease was in group IV (combination) from 174.8±3.7 to 136.1±2.4 mmHg (22%) ($p<0.0001$); in group III (trandolapril) from 165.8±2.7 to 137.5±2.9 mmHg (17%) ($p = 0.0002$); and in group II (LU-135252) and from 169.1±3.1 to 147.8±2.5 mmHg (12%) ($p = 0.0004$). Glucose levels in plasma decreased significantly after 6 wk of treatment. Maximum decrease was in group IV: from 501.0±42.8 to 178.6±7.3 mg/dL (62%) ($p<0.0001$); in group III from 428.2±47.7 to 146.8±5.6 mg/dL (63%) ($p<0.0001$); and in group II from 491.2±39.3 to 272.2±28.3 mg/dL (42%) ($p = 0.0002$). Conclusion: The SBP decrease was additive when both drugs were given together. Thus, combination of ETA antagonist and ACE inhibitor appears to offer a rational fixed-dose antihypertensive therapy, which is superior to that of either drug alone. The decrease in glucose level, which was the least impressive while on LU-135252 alone, was more prominent during combination after 2 wk, although without further decrease.
IT **171714-84-4**, LU-135252
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)(combination therapy with endothelin A antagonist LU-135252 and trandolapril, had high rational antihypertensive, hypoglycemic effect than alone via decrease in glucose, blood pressure in Cohen Rosenthal diabetic hypertensive rat model)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

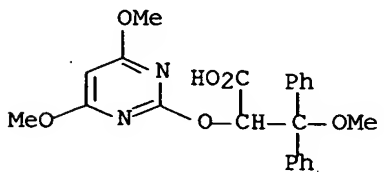


RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD

L11 ANSWER 15 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2005:321453 CAPLUS Full-text
DN 144:233017
TI Synthesis of darusentan, an ETA selective endothelin receptor antagonist
AU Guo, Feng; Chen, Yi-qi; Ji, Min; Hua, Wei-yi
CS Center of Drug Discovery, China Pharmaceutical University, Nanjing, 210009, Peop. Rep. China
SO Zhongguo Xinyao Zazhi (2005), 14(2), 172-173
CODEN: ZXZHA6; ISSN: 1003-3734
PB Zhongguo Xinyao Zazhishe
DT Journal
LA Chinese
AB The synthesis of darusentan, an ETA selective endothelin receptor antagonist, is reported. Using di-Ph ketone as a starting material, the target compound was synthesized via several steps, involving in non-solvent Darzens condensation with Et chloroacetate, methanolysis catalyzed by p-toluene sulfonic acid, nucleophilic substitution with 2-chloro-4,6-dimethoxypyrimidine catalyzed by sulfinate, and alkaline hydrolysis. The chemical structure of the target compound was verified using IR, 1H-NMR and MS. The easily controlled and low cost process for the synthesis of darusentan achieved a total yield of 53.5%.
IT **876148-92-4P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of darusentan, an ETA selective endothelin receptor antagonist via non-solvent Darzens condensation, methanolysis, nucleophilic substitution and alkaline hydrolysis)
RN 876148-92-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, ethyl ester (9CI) (CA INDEX NAME)



IT **178306-46-2P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(synthesis of darusentan, an ETA selective endothelin receptor antagonist via non-solvent Darzens condensation, methanolysis, nucleophilic substitution and alkaline hydrolysis)
RN 178306-46-2 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl- (9CI) (CA INDEX NAME)



L11 ANSWER 16 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2005:300237 CAPLUS Full-text
DN 142:360858
TI Iloprost in combination therapies for the treatment of pulmonary arterial hypertension
IN Santel, Donald J.
PA Cotherix, Inc., USA
SO PCT Int. Appl., 13 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2005030187	A2	20050407	WO 2004-US31149	20040921
	WO 2005030187	A3	20050623		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2005101608	A1	20050512	US 2004-945255	20040920
PRAI	US 2003-505653P	P	20030924		

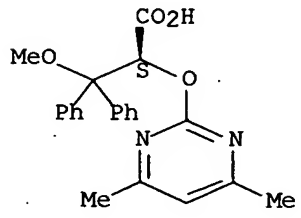
AB Preferred embodiments of the present invention are related to novel therapeutic drug combinations and methods for treating pulmonary arterial hypertension. More particularly, aspects of the present invention are related to using a combination of iloprost and at least one addnl. agent, selected from the group consisting of an endothelin receptor antagonist and, e.g. bosentan, a PDE inhibitor, e.g. sildenafil (no data).

IT **177036-94-1**, Ambrisentan
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(iloprost in combination therapies for treatment of pulmonary arterial hypertension)

RN 177036-94-1 CAPLUS

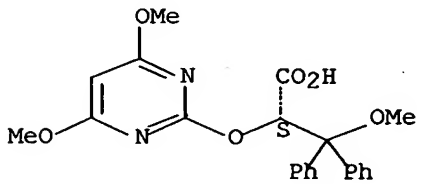
CN Benzenepropanoic acid, α-[(4,6-dimethyl-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L11 ANSWER 17 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2005:133408 CAPLUS Full-text
DN 142:423728
TI Amelioration of microcirculatory damage by an endothelin A receptor antagonist in a rat model of reversible acute liver failure
AU Palmes, Daniel; Skawran, Sebastian; Stratmann, Udo; Armann, Barbara; Minin, Evgeny; Herbst, Hermann; Spiegel, Hans-Ullrich
CS Surgical Research, Department of General Surgery, Muenster University Hospital, Muenster, 48149, Germany
SO Journal of Hepatology (2005), 42(3), 350-357
CODEN: JOHEEC; ISSN: 0168-8278
PB Elsevier B.V.
DT Journal
LA English
AB Background/Aims: Hepatocellular damage in acute liver failure (ALF) is aggravated by proinflammatory and cytotoxic mediators released from sinusoidal-lining cells. We studied a selective endothelin A receptor (ETAR) antagonist for its potential influence on the microcirculation in the setting of ALF. Methods: Seventy Wistar rats were divided into five groups: (I) induction of ALF by a 70% liver resection combined with injection of 400 μg/kg endotoxin, (II) ALF treated with the ETAR antagonist LU 135252 (1 mg/kg b.w. i.v.), (III) sham operation, (IV) injection of endotoxin, (V) 70% liver resection. Liver microcirculation was measured by intravital microscopy. Parenchymal injury, growth fractions, endothelin (ET)-1 and ETAR were studied by histol. and immunohistol. Survival, liver function, and morphol. were followed up to 14 days. Results: 100% mortality, impaired liver function, widespread endothelial lesions, highest ET-1 and ETAR levels, a decreased perfusion rate, reduced sinusoidal diameter, as well as an increase in both leukocyte-endothelium interactions and sinusoidal blood flow were observed after induction of ALF. ETAR antagonist-treated rats showed decreased ET-1 and ETAR levels as well as improved microcirculatory function, morphol., liver function, and 85% survival. Conclusions: Microcirculatory disturbances correlate with liver dysfunction in ALF. ETAR blockade represents a new therapeutic approach to ALF by reducing microcirculatory lesions and their sequelae.
IT **171714-84-4**, Darusentan
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(endothelin A receptor antagonist Darusentan decreased microcirculatory damage, ET-1 and ETAR levels and improved microcirculatory function, morphol., liver function and survival in rat model of reversible acute liver failure)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

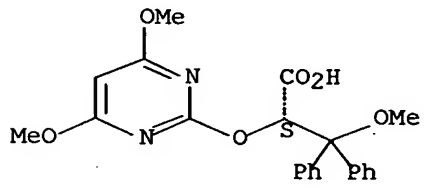
Absolute stereochemistry.



RE.CNT 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 18 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2005:38451 CAPLUS Full-text
DN 142:190764
TI Inhalation of the endothelin-A receptor antagonist LU-135252 at various doses in experimental acute lung injury
AU Deja, Maria; Busch, Thilo; Wolf, Steffen; Donaubauer, Bernd; Petersen, Bodil; Skomrock, Joerg; Boemke, Willehad; Kaisers, Udo
CS Department of Anesthesiology and Intensive Care Medicine, University Medical Center, Berlin, Germany
SO Journal of Cardiovascular Pharmacology (2004), 44(Suppl. 1), S151-S155
CODEN: JCPCDT; ISSN: 0160-2446
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB The authors studied the effects of the inhaled endothelin-A receptor antagonist LU-135252 at different doses on hemodynamics and gas exchange in an animal model of acute lung injury. Thirty-six piglets (27 ± 1 kg) were anesthetized, mech. ventilated (FiO2 1.0), and surfactant-depleted by repeated lung lavage. The animals were randomly assigned to receive either nebulized LU-135252 for 30 min at a dose of 0.3 mg/kg (n = 12), or at a dose of 3.0 mg/kg (n = 12); n = 12 animals received no further treatment (Controls). Induction of acute lung injury decreased PaO2 from 566 ± 8 mmHg to 53 ± 2 mmHg (mean ± SEM) and increased intrapulmonary shunt (QS/QT) from 13 ± 1% to 57 ± 2%. Inhalation of LU-135252 at either dose induced a significant and sustained increase in PaO2 (0.3 mg/kg: 349 ± 39 mmHg; 3.0 mg/kg: 219 ± 40 mmHg), and a significant decrease in QS/QT (0.3 mg/kg: 19 ± 2%; 3.0 mg/kg: 27 ± 3%) when compared with Controls (PaO2: 50 ± 3 mmHg, QS/QT: 50 ± 5%) ($P < 0.05$; values at 4 h). Mean pulmonary artery pressure in LU-135252-treated animals (0.3 mg/kg: 31 ± 2 mmHg; 3.0 mg/kg: 30 ± 1 mmHg) was significantly lower than in Controls (40 ± 2 mmHg), while there were no differences in mean arterial pressure and cardiac output. The authors conclude that inhalation of LU-135252 at either dose improved gas exchange and hemodynamics comparably, indicating that the lower dose was already sufficient to block the majority of endothelin-A receptors in ventilated regions of the injured lung.
IT **171714-84-4**, LU-135252
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhalation of endothelin-A receptor antagonist LU-135252 at various doses in exptl. acute lung injury)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

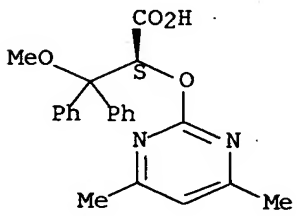
Absolute stereochemistry.



RE.CNT 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 19 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2005:38438 CAPLUS Full-text
DN 142:190762
TI Endothelin-A receptor blockade improves postischemic hepatic microhemodynamics
AU Uhlmann, Dirk; Glasser, Sebastian; Lauer, Heike; Ludwig, Stefan; Gaebel, Gabor; Serr, Frederick; Hauss, Johann; Witzigmann, Helmut
CS Second Department of Surgery, University of Leipzig, Germany
SO Journal of Cardiovascular Pharmacology (2004), 44(Suppl. 1), S103-S104
CODEN: JCPCDT; ISSN: 0160-2446
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB The aim of this study was to investigate a possible protective role of a selective endothelin-A receptor antagonist on hepatic microcirculation after ischemia/reperfusion. In a rat model, warm ischemia of the left liver lobe was induced for 90 min under i.p. anesthesia with xylazine and ketamine. Sham-operated and untreated ischemic groups and a group treated with BSF 208075 were investigated. The effect of the endothelin-A receptor antagonist on ischemia/reperfusion was assessed by in-vivo microscopy and measurement of aspartate aminotransferase and alanine aminotransferase levels. In the untreated group, sinusoidal constriction to 70% of basal diams. was observed, leading to a significant decrease in perfusion rate. In addition, the authors found an increased percentage of stagnant leukocytes and platelets in sinusoids and in postsinusoidal venules ($P < 0.05$). A significant increase in liver enzymes was detected 6 h after reperfusion ($P < 0.05$). In the treatment group, sinusoidal diams. were maintained at 108%, and perfusion rate was significantly increased ($P < 0.05$). Hepatocellular damage was decreased and leukocyte and platelet-endothelium interactions were reduced ($P < 0.05$). The authors' results provide evidence that the new therapeutic approach using an endothelin-A receptor antagonist is effective in reducing hepatic ischemia/reperfusion injury. It could be shown for the first time that endothelin receptor blockade also influences platelet-endothelium interactions.
IT **177036-94-1**, BSF 208075
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(endothelin-A receptor blockade improves postischemic hepatic microhemodynamics)
RN 177036-94-1 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethyl-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

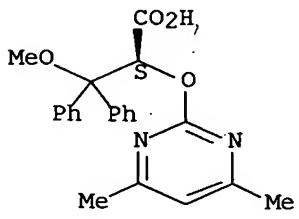
Absolute stereochemistry.



RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 20 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2005:38437 CAPLUS Full-text
DN 142:190761
TI Changes of vasoregulatory gene expression following hepatic ischemia/reperfusion and treatment with endothelin-A receptor blockade
AU Uhlmann, Dirk; Gaebel, Gabor; Teupser, Daniel; Armann, Barbara; Tannapfel, Andrea; Ludwig, Stefan; Pietsch, Uta-Carolin; Fiedler, Georg Martin; Hauss, Johann; Witzigmann, Helmut
CS Second Department of Surgery, University of Leipzig, Leipzig, Germany
SO Journal of Cardiovascular Pharmacology (2004), 44(Suppl. 1), S100-S102
CODEN: JCPCDT; ISSN: 0160-2446
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB The objective of this study was to investigate the effect of a specific endothelin-A receptor antagonist on mRNA expression of genes encoding vasoactive mediators and proinflammatory cytokines following complete vascular exclusion of the porcine liver. Fourteen adult German Landrace pigs were subjected to 120 min of warm hepatic ischemia by total vascular exclusion. The animals were divided into 2 groups: the control group received saline solution and the therapy group was given the selective endothelin-A receptor antagonist BSF 208075. Liver tissue samples were collected 1 h after reperfusion and mRNA expression for preproendothelin-1, prointerleukin-1β, prointerleukin-6, pro-tumor necrosis factor-α and endothelial nitric oxide synthase was analyzed quant. using the TaqMan system. Addnl., immunohistochem. anal. using a semiquant. score for endothelin-1 and endothelin-A receptor was performed. One hour after reperfusion, quant. reverse transcriptase-polymerase chain reaction revealed significantly lower expression of preproendothelin-1, pro-tumor necrosis factor-α, and prointerleukin-6 in the therapy group compared to controls. Immunohistochem. anal. demonstrated significantly reduced endothelin-1 immunostaining after therapy. Treatment with the selective endothelin-A receptor antagonist exerts a protective effect on the microcirculation after liver ischemia and reperfusion. The authors were able to show that the endothelin-A receptor antagonist not only has effects on the expression of vasoactive genes, it also decreases gene expression of proinflammatory cytokines such as tumor necrosis factor-α and interleukin-6.
IT **177036-94-1**, BSF 208075
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(changes of vasoregulatory gene expression following hepatic ischemia/reperfusion and treatment with endothelin-A receptor blockade)
RN 177036-94-1 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethyl-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 21 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2005:29217 CAPLUS Full-text
DN 142:141234
TI Delivering polymerized therapeutic agent compositions
IN Waugh, Jacob; Razavi, Mahmood; Rhee, Ceron; Bryant, Clifford
PA Polycord, Inc., USA
SO PCT Int. Appl., 79 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2005002597	A1	20050113	WO 2004-US21453	20040702
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2005074425	A1	20050407	US 2004-884226	20040702
PRAI	US 2003-485076P	P	20030702		
	US 2004-884226	A	20040702		

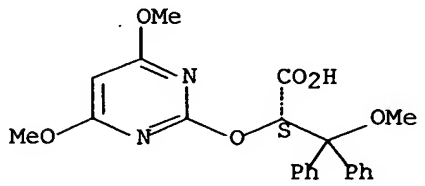
AB A method for delivering polymerized therapeutic agents and their compns. are disclosed. The various polymers take advantage of the functional domains found in a variety of therapeutic agents. The polymerized therapeutic agent compns. are prepared by covalently linking the agent to a biocompatible backbone either directly or through backbone conjugates/monomers. The polymerized therapeutic agent compns. of the invention have highly desirable properties, which make them particularly well suited for use in biol. and biomedical applications. An example is polyaspartate with rofecoxib-OH derivative ester side chains.

IT **171714-84-4**, LU135252
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(delivering polymerized therapeutic agent compns.)

RN 171714-84-4 CAPLUS

CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

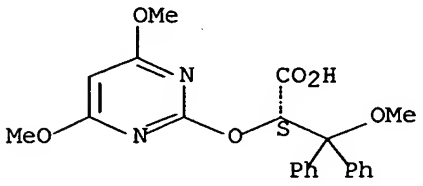
L11 ANSWER 22 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2004:971456 CAPLUS Full-text
DN 142:253609
TI Effects of systemic endothelin A receptor antagonism in various vascular beds in men: In vivo interactions of the major blood pressure-regulating systems and associations with the GNB3 C825T polymorphism
AU Mitchell, Anna; Lueckebergfeld, Birte; Buehrmann, Sandra; Rushentsova, Uljana; Nuernberger, Jens; Siffert, Winfried; Schaefers, Rafael F.; Philipp, Thomas; Wenzel, Rene R.
CS Department of Nephrology and Hypertension and Institute of Pharmacology, Essen University Hospital, Germany
SO Clinical Pharmacology & Therapeutics (St. Louis, MO, United States) (2004), 76(5), 396-408
CODEN: CLPTAT; ISSN: 0009-9236
PB Elsevier Inc.
DT Journal
LA English
AB We used the orally available endothelin A (ETA) receptor antagonist darusentan to characterize interactions between the major blood pressure-regulating systems in healthy men. Mediators of the endothelin system, the sympathetic nervous system, and the renin-angiotensin system act via G protein-coupled receptors with a possible involvement of the G-protein β3 subunit (GNB3) C825T polymorphism. We studied the influence of this polymorphism on the responses to ETA antagonism in the presence of endothelin 1 (ET-1), norepinephrine (NA), and angiotensin II (ANGII). Thirty-seven individuals were included in a randomized, double-blind, placebo-controlled, crossover trial with 100 mg darusentan. Systemic hemodynamics and plasma ET-1, NA, and ANGII concns. were assessed. Local studies were performed in the dorsal hand veins (n = 18) and skin microcirculation (n = 12), resp. Darusentan lowered systolic and diastolic blood pressure (P < .001 vs. placebo) without any differences according to genotype (mean maximum Δ systolic blood pressure, −7 ± 2 mm Hg for CT/TT vs. −5 ± 3 mm Hg for CC, P = .37; mean maximum Δ diastolic blood pressure, −3 ± 2 mm Hg for CT/TT vs. −4 ± 2 mm Hg for CC, P = .96). Venoconstriction to ET-1 and NA was not affected by ETA blockade in either group; however, carriers of the 825T allele demonstrated a markedly enhanced venoconstriction to ET-1 and NA (median effective concentration [ED50] for ET-1 after darusentan [placebo]: 2.5 ± 0.2 pmol/min for CT/TT [2.7 ± 0.3 pmol/min], P = .42; 3.9 ± 0.6 pmol/min for CC [4.6 ± 0.3 pmol/min], P = .42; P = .046 [P = .0005] for CT/TT vs. CC) (ED50 for NA after darusentan [placebo]: 5.2 ± 1.2 ng/min for CT/TT [7.3 ± 1.2 ng/min], P = .20; 32.9 ± 7.1 ng/min for CC [19.7 ± 5.5 ng/min], P = .75; P = .0008 [P = .026] for CT/TT vs. CC). Darusentan dilated veins at baseline in CC homozygous subjects (+0.21 ± 0.05 mm, P = .004 vs. placebo). Systemic ETA antagonism inhibited constriction to ET-1 and also to NA and ANGII in the skin microcirculation without differences according to genotype (ET-1, P = .017 for all individuals vs. placebo; NA, P = .0005; and ANGII, P = .002). GNB3 C825T allele carrier status did not influence systemic hemodynamic or local vascular responses to ETA blockade with darusentan in young, healthy men. However, it determined venoconstriction to exogenous ET-1 and NA. Darusentan markedly inhibited not only ET-1-induced but also NA-induced and ANGII-induced vasoconstriction in the skin microcirculation. In contrast, it had no effects on either ET-1-mediated or NA-mediated venoconstriction, indicating that, in the presence of high local ET-1 concns., constrictive endothelin B receptors may be of greater importance in the venous vasculature than has been recognized so far.
IT **171714-84-4**, Darusentan
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(GNB3 C825T polymorphism did not affect systemic hemodynamic or local vascular response to darusentan which inhibited ET-1, NA, ANGII induced

vasoconstriction but not ET-1, NA induced venoconstriction which enhanced with 825T allele in human)

RN 171714-84-4 CAPLUS

CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 23 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2004:878302 CAPLUS Full-text
DN 141:360694
TI Combination therapy using an 11β-hydroxysteroid dehydrogenase type 1 inhibitor and an antihypertensive agent for the treatment of metabolic syndrome and related diseases and disorders
IN Kampen, Gita Camilla Tejlgaard; Andersen, Henrik Sune
PA Novo Nordisk A/S, Den.
SO PCT Int. Appl., 297 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 7

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004089416	A2	20041021	WO 2004-DK254	20040406
	WO 2004089416	A3	20050303		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
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	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR				
PRAI	DK 2003-565	A	20030411		
	DK 2003-566	A	20030411		
	DK 2003-567	A	20030411		
	DK 2003-569	A	20030411		
	DK 2003-570	A	20030411		
	DK 2003-571	A	20030411		
	US 2003-467284P	P	20030502		
	US 2003-467362P	P	20030502		
	US 2003-467363P	P	20030502		
	US 2003-467437P	P	20030502		
	US 2003-467453P	P	20030502		
	US 2003-467800P	P	20030502		
	DK 2003-776	A	20030522		
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	US 2003-475157P	P	20030602		
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	DK 2003-988	A	20030630		
	DK 2003-989	A	20030630		
	DK 2003-990	A	20030630		
	DK 2003-998	A	20030702		
	US 2003-486078P	P	20030710		
	US 2003-486094P	P	20030710		
	US 2003-486095P	P	20030710		
	US 2003-486097P	P	20030710		
	US 2003-486098P	P	20030710		
	DK 2003-1910	A	20031222		
	DK 2004-9	A	20040106		
	US 2004-537099P	P	20040116		

WO 2004-DK254 W 20040406

OS MARPAT 141:360694

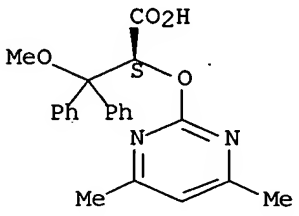
AB The invention discloses combination therapy comprising the administration of an 11β-hydroxysteroid dehydrogenase type 1 inhibitor and an antihypertensive agent useful for treating, preventing and reducing the risk of developing insulin resistance, dyslipidemia, obesity, hypertension and other related diseases and disorders.

IT **177036-94-1**, Ambrisentan
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hydroxysteroid dehydrogenase inhibitor-antihypertensive agent combination for treatment of metabolic syndrome and related conditions)

RN 177036-94-1 CAPLUS

CN Benzenepropanoic acid, α-[(4,6-dimethyl-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L11 ANSWER 24 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2004:780354 CAPLUS Full-text
DN 141:289052
TI Combination of an aldosterone receptor antagonist and an endothelin receptor antagonist and/or endothelin converting enzyme inhibitor for the treatment of cardiovascular and other conditions
IN McMahon, Ellen G.; Rudolph, Amy E.
PA Pharmacia Corporation, USA
SO U.S. Pat. Appl. Publ., 42 pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2004186083	A1	20040923	US 2004-803818	20040318
WO 2004082637	A2	20040930	WO 2004-US8250	20040318

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

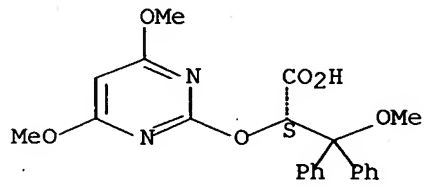
PRAI US 2003-455580P P 20030318

AB The invention describes combinations, compns., and therapeutic methods of treatment and/or prophylaxis of hypertension, cardiovascular disease, renal dysfunction, edema, cerebrovascular disease, or insulinopathy pathol. conditions in a subject, wherein the methods comprise the administration of a combination of one or more aldosterone receptor antagonists and one or more endothelin receptor antagonist and/or ECE inhibitors.

IT **171714-84-4**, Darusentan **177036-94-1**, Ambrisentan
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination of aldosterone receptor antagonist and endothelin receptor antagonist and/or endothelin converting enzyme inhibitor for treatment of cardiovascular and other conditions)

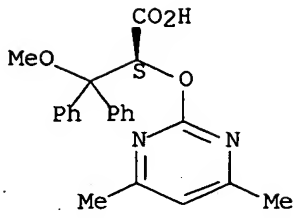
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



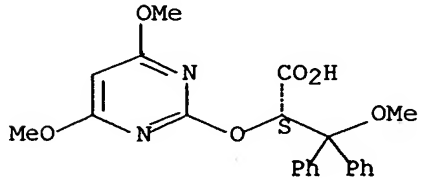
RN 177036-94-1 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethyl-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.


CO2H
MeO
S
O
Ph
Ph
N
N
Me
Me

L11 ANSWER 25 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2004:600776 CAPLUS Full-text
DN 142:169478
TI Long-term effects of darusentan on left-ventricular remodeling and clinical outcomes in the endothelinA receptor antagonist trial in heart failure (EARTH): randomised, double-blind, placebo-controlled trial
AU Anand, Inder; McMurray, John; Cohn, Jay N.; Konstam, Marvin A.; Notter, Thomas; Quitzau, Kurt; Ruschitzka, Frank; Luscher, Thomas F.
CS Veterans Affairs Medical Center, University of Minnesota, Minneapolis, MN, USA
SO Lancet (2004), 364(9431), 347-354
CODEN: LANCAO; ISSN: 0140-6736
PB Elsevier
DT Journal
LA English
AB Endothelin-receptor blockade provides hemodynamic benefit in exptl. and clin. heart failure. We aimed to measure the effects of long-term endothelin-blockade on left-ventricular (LV) remodeling and clin. outcomes in patients with chronic heart failure. Six hundred forty-two patients with chronic heart failure were assigned the oral endothelinA-antagonist darusentan at 10, 25, 50, 100, or 300 mg daily or placebo for 24 wk in addition to standard therapy in a randomized, double-blind, placebo-controlled trial. In the 50-300 mg groups, darusentan was uptitrated over 6 wk. Primary endpoint was change in LV end-systolic volume (LVESV) at 24 wk from baseline, measured by MRI. All patients for whom assessable MRI scans were available at baseline and follow-up were included in the anal. Darusentan was well tolerated. LVESV could be assessed in 485 (76%) patients with paired MRI data at baseline and 6 mo. The change in LVESV was not significantly different from that with placebo at any dose (mean difference from placebo 1.27 mL [95% CI -9.9-12.4] with 10 mg dose, -1.84 mL [-13.0-9.3] with 25 mg, -5.68 mL [-16.9-5.6] with 50 mg, -4.05 mL [-15.5-7.4] with 100 mg, and -4.34 mL [-15.7-7.0] with 300 mg). Heart failure worsened in 71 (11.1%) patients, and 30 (4.7%) died during the study with no difference between groups. EndothelinA blockade with darusentan did not improve cardiac remodeling or clin. symptoms or outcomes in patients with chronic heart failure receiving an angiotensin-converting-enzyme inhibitor, β blocker, or aldosterone antagonist. Thus, endothelinA blockade is unlikely to be useful as an add-on treatment in such patients.
IT **171714-84-4**, Darusentan
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(endothelinA antagonist, darusentan did not improve cardiac remodeling or clin. symptoms or outcomes in patient with chronic heart failure receiving angiotensin-converting-enzyme inhibitor, β blocker or aldosterone antagonist)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 26 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2004:354796 CAPLUS Full-text
DN 140:368653
TI Endothelin receptor antagonist-EGF receptor tyrosine kinase inhibitor combination for the treatment of cancer
IN Boyle, Francis Thomas; Curwen, Jon Owen; Gallagher, Neil James; Hancox, Ursula Joy; Hughes, Andrew Mark; Johnstone, Donna; Taylor, Sian Tomiko; Tonge, David William
PA Astrazeneca AB, Swed.; Astrazeneca UK Limited
SO PCT Int. Appl., 24 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004035057	A1	20040429	WO 2003-GB4347	20031007
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	CA 2501959	AA	20040429	CA 2003-2501959	20031007
	AU 2003269259	A1	20040504	AU 2003-269259	20031007
	EP 1553950	A1	20050720	EP 2003-751038	20031007
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
	BR 2003015140	A	20050816	BR 2003-15140	20031007
	NO 2005001658	A	20050506	NO 2005-1658	20050404
PRAI	GB 2002-23854	A	20021012		
	WO 2003-GB4347	W	20031007		

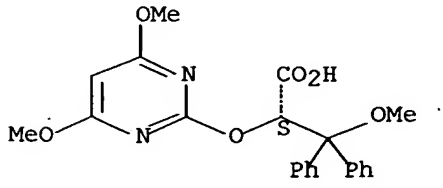
AB A combination, comprising an endothelin receptor antagonist (e.g. ZD4054), or a pharmaceutically acceptable salt thereof, and an EGF receptor tyrosine kinase inhibitor (e.g. ZD1839), or a pharmaceutically acceptable salt thereof, is described. The combination of the invention is useful for the treatment of cancer, e.g. prostate cancer.

IT **171714-84-4**, Darusentan **177036-94-1**, Ambrisentan
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(endothelin receptor antagonist-EGF receptor tyrosine kinase inhibitor combination for treatment of cancer)

RN 171714-84-4 CAPLUS

CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

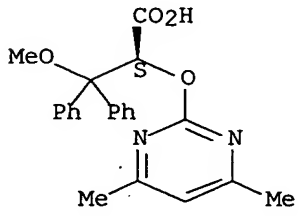
Absolute stereochemistry.



RN 177036-94-1 CAPLUS

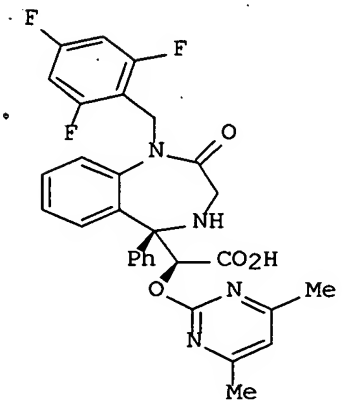
CN Benzenepropanoic acid, α-[(4,6-dimethyl-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 27 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2004:344184 CAPLUS Full-text
DN 141:89068
TI Novel Benzo[1,4]diazepin-2-one Derivatives as Endothelin Receptor Antagonists
AU Bolli, Martin H.; Marfurt, Judith; Grisostomi, Corinna; Boss, Christoph; Binkert, Christoph; Hess, Patrick; Treiber, Alexander; Thorin, Eric; Morrison, Keith; Buchmann, Stephan; Bur, Daniel; Ramuz, Henri; Clozel, Martine; Fischli, Walter; Weller, Thomas
CS Drug Discovery Chemistry and Preclinical Research, Actelion Pharmaceuticals Ltd., Allschwil, CH-4123, Switz.
SO Journal of Medicinal Chemistry (2004), 47(11), 2776-2795
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
GI



I

AB Since its discovery in 1988 by Yanagisawa et al., endothelin (ET), a potent vasoconstrictor, has been widely implicated in the pathophysiol. of cardiovascular, cerebrovascular, and renal diseases. Many research groups have embarked on the discovery and development of ET receptor antagonists for the treatment of such diseases. While several compds., e.g., ambrisentan, are in late clin. trials for various indications, one compound (bosentan, Tracleer) is being marketed to treat pulmonary arterial hypertension. Inspired by the structure of ambrisentan, a novel class of ET receptor antagonists based on a 1,3,4,5-tetrahydro-1H- benzo[e][1,4]diazepin-2-one scaffold was designed. The preparation as well as the in vitro and in vivo structure-activity relationships of these derivs. are reported. Potent dual ETA/ETB receptor antagonists with affinities in the low nanomolar range have been identified. In addition, several compds. efficiently reduced arterial blood pressure after oral administration to Dahl salt-sensitive rats. In this animal model, the efficacy of (αR,5R)-rel-α-[(4,6-dimethyl-2-pyrimidinyl)oxy]-2,3,4,5- tetrahydro-2-oxo-5-phenyl-1-[(2,4,6-trifluorophenyl)methyl]-1H-1,4-benzodiazepine-5-acetic acid (I) was superior to that of racemic ambrisentan.

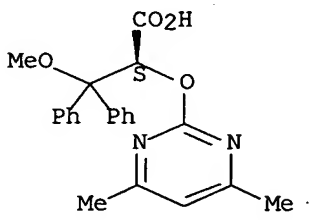
IT **177036-94-1DP**, Ambrisentan, derivs. **713516-99-5P**, (±)-Ambrisentan
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of benzo[1,4]diazepin-2-one derivs. and study of their

activity
as endothelin receptor antagonists)

RN 177036-94-1 CAPLUS

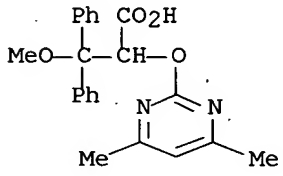
CN Benzenepropanoic acid, α-[(4,6-dimethyl-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 713516-99-5 CAPLUS

CN Benzenepropanoic acid, α-[(4,6-dimethyl-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl- (9CI) (CA INDEX NAME)



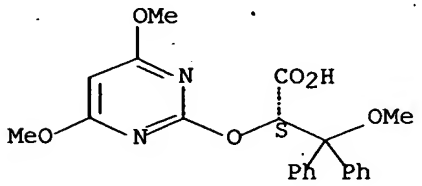
RE.CNT 84 THERE ARE 84 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 28 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2004:331974 CAPLUS Full-text
DN 140:332519
TI 5-HT1B/1D receptor agonists for the treatment of headache resulting from administering an endothelin receptor antagonist
IN Curwen, Jon Owen; Hughes, Andrew Mark; Johnstone, Donna; Morris, Clive Dylan
PA Astrazeneca AB, Swed.; Astrazeneca Uk Limited
SO PCT Int. Appl., 25 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004032922	A1	20040422	WO 2003-GB4338	20031006
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	AU 2003274307	A1	20040504	AU 2003-274307	20031006
	EP 1551395	A1	20050713	EP 2003-758297	20031006
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
	JP 2006508933	T2	20060316	JP 2004-542622	20031006
	US 2006009512	A1	20060112	US 2005-530232	20050404
PRAI	GB 2002-23367	A	20021009		
	WO 2003-GB4338	W	20031006		

AB The invention discloses the use of a 5-HT1B/1D receptor agonist in the treatment or prevention of headache that results from administering an endothelin receptor antagonist. The invention also discloses a combination comprising an endothelin receptor antagonist and a 5-HT1B/1D receptor agonist.
IT **171714-84-4**, Darusentan **177036-94-1**, Ambrisentan
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(5-HT1B/1D receptor agonists for the treatment of headache resulting from administering an endothelin receptor antagonist)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

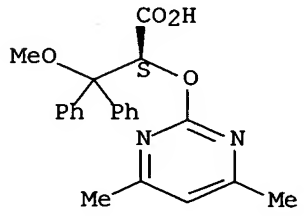
Absolute stereochemistry.



RN 177036-94-1 CAPLUS

CN Benzenepropanoic acid, α-[(4,6-dimethyl-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

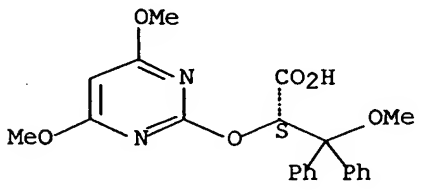
Absolute stereochemistry.



RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 29 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2004:314794 CAPLUS Full-text
DN 141:307257
TI ACE-inhibition is superior to endothelin A receptor blockade in preventing abnormal capillary supply and fibrosis of the heart in experimental diabetes
AU Gross, M.-L.; Heiss, N.; Weckbach, M.; Hansen, A.; El-Shakmak, A.; Szabo, A.; Muenter, K.; Ritz, E.; Amann, K.
CS Department of Pathology, University of Heidelberg, Heidelberg, Germany
SO Diabetologia (2004), 47(2), 316-324
CODEN: DBTGAJ; ISSN: 0012-186X
PB Springer-Verlag
DT Journal
LA English
AB Aims/hypothesis: There is little information whether cardiac capillary supply is deranged in diabetes. Hyperglycemia is a potent stimulus for endothelin-1 (ET-1) production We therefore hypothesized that increased ET-1 production in Streptozotocin-induced Type 1 diabetes causes abnormalities of cardiac capillaries and the aorta. To this end we compared the effects of an ET receptor A blocker (ETA-RB) with that of an ACE-inhibitor (ACE-i) or their combination in rats with Streptozotocin (STZ) diabetes. Methods: Sprague Dawley rats were injected with 65 mg STZ i.v. and subsequently developed diabetes. Rats were left untreated or received daily either the ACE-i Trandolapril, the ETA-RB Darusentan or a combination of both. After 6 mo the experiment was terminated and the heart and the aorta were investigated using quant. morphol. techniques. Results: ACE-i but not ETA-RB lowered blood pressure in STZ Type 1 diabetic rats. Capillary length d. was lower in untreated STZ diabetic rats (2932±128 mm/mm3) compared to non-diabetic control rats (3410±252 mm/mm3). Treatment with ACE-i (3568±431 mm/mm3), but not with ETA-RB (2893±192 mm/mm3), prevented the decrease in capillary supply. Volume d. of the myocardial interstitium was higher in untreated STZ diabetic rats (0.86±0.04%) compared to non-diabetic control rats (0.36±0.06%). In all three intervention groups the values were lower (ACE-i: 0.53±0.05%, ETA-RB: 0.7±0.08% and combination: 0.69±0.1). Conclusion/interpretation: Our study identifies a capillary defect of the heart in STZ diabetes, i.e. decreased capillary supply. This abnormality was reversed by ACE-i, but not by ETA-R blockade. A similar trend, although not complete normalization, was seen in cardiac fibrosis.
IT **171714-84-4**, Darusentan
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ACE-i trandolapril treatment was more effective than ETA-RB darusentan in preventing interstitial fibrosis and capillary defect of heart in STZ Type 1 diabetic rat)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 30 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2004:291975 CAPLUS Full-text
DN 140:315088
TI Endothelin antagonists for treating Alzheimer's disease and dementias of vascular origin
IN Gulati, Anil
PA The Board of Trustees of the University of Illinois, USA
SO PCT Int. Appl., 89 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

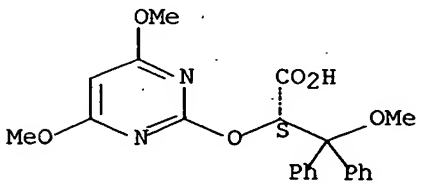
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004028634	A1	20040408	WO 2003-US28212	20030910
	WO 2004028634	C2	20040708		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	AU 2003270446	A1	20040419	AU 2003-270446	20030910
	US 2004092427	A1	20040513	US 2003-659579	20030910
PRAI	US 2002-413539P	P	20020925		
	WO 2003-US28212	W	20030910		

AB A composition and method of treating Alzheimer's disease or a dementia of vascular origin are disclosed. The composition and method utilize an endothelin antagonist as the active agent to treat Alzheimer's desease or a dementia of vascular origin in mammals, including humans.

IT **171714-84-4**, LU 135252 **177036-94-1**, BSF 208075
531491-64-2
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(endothelin antagonists for treating Alzheimer's disease and vascular dementia)

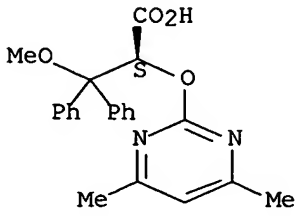
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 177036-94-1 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethyl-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

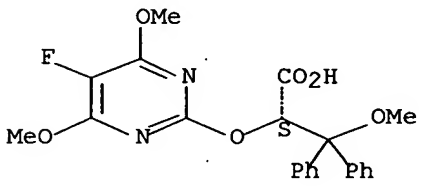
Absolute stereochemistry.



RN 531491-64-2 CAPLUS

CN Benzenepropanoic acid, α-[(5-fluoro-4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

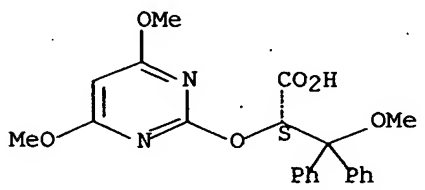
Absolute stereochemistry.



RE.CNT 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 31 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2004:26408 CAPLUS Full-text
DN 140:301554
TI Endothelin A Receptor Antagonism in Experimental Congestive Heart Failure Results in Augmentation of the Renin-Angiotensin System and Sustained Sodium Retention
AU Schirger, John A.; Chen, Horng H.; Jougasaki, Michihisa; Lisy, Ondrej; Boerrigter, Guido; Cataliotti, Alessandro; Burnett, John C.
CS Cardiorenal Research Laboratory, Division of Cardiovascular Diseases and Department of Physiology, Mayo Clinic and Foundation, Rochester, MN, USA
SO Circulation (2004), 109(2), 249-254
CODEN: CIRCAZ; ISSN: 0009-7322
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB Background- While both the endothelin-1 (ET-1) and renin-angiotensin systems (RAS) are activated in congestive heart failure (CHF), the temporal sequence of this activation remains unclear. Understanding this pattern of neurohumoral activation may aid in understanding the significance of ET-1 in CHF and provide strategies for ET-1 antagonism. Although acute endothelin (ET) receptor antagonism improves systemic hemodynamics in CHF, clin. trials with chronic ET receptor antagonism report worsening CHF symptoms. Methods and Results- In a canine model of progressive left ventricular dysfunction, the authors demonstrated activation of myocardial and plasma ET-1 without activation of the RAS during transition to overt CHF, suggesting that ET-1 contributes to this transition. The authors next evaluated the effects of chronic oral ET-A receptor antagonism on neurohumoral function, renal hemodynamics, and sodium excretion in pacing-induced CHF. After 7 days of treatment with ET-A receptor antagonism (with LU135252), sodium excretion did not improve in treated vs. untreated CHF. Furthermore, both plasma renin activity and plasma ET-1 increased with ET-A receptor blockade. Conclusions- Activation of the myocardial and plasma ET-1 systems precedes activation of the myocardial and plasma RAS in CHF. ET-A receptor antagonism in exptl. CHF further activates the RAS without improving sodium excretion. These findings suggest an important role for ET-1 in the progression of CHF and a potential mechanism for the exacerbation of CHF symptoms observed in clin. trials with chronic ET receptor antagonism. Further studies with combined modulation of the ET and other neurohumoral systems in CHF are required.
IT **171714-84-4**, LU135252
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(endothelin A receptor antagonism in exptl. congestive heart failure results in augmentation of renin-angiotensin system and sustained sodium retention)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 32 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2003:1007851 CAPLUS Full-text
DN 140:53448
TI Method and composition for potentiating the antipyretic action of a nonopioid analgesic
IN Gulati, Anil
PA USA
SO U.S. Pat. Appl. Publ., 55 pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003236235	A1	20031225	US 2003-459905	20030612
WO 2004000357	A1	20031231	WO 2003-US19151	20030617

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

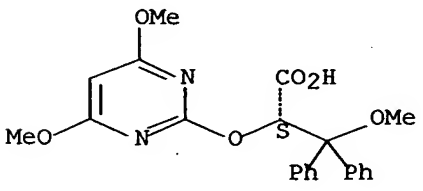
AU 2003279180	A1	20040106	AU 2003-279180	20030617
PRAI US 2002-390045P	P	20020619		
WO 2003-US19151	W	20030617		

AB A composition and method of treating fever, and optionally treating pain, are disclosed. The composition and method utilize a non-opioid analgesic and an endothelin antagonist as active agents to treat fever in mammals, including humans. The composition also is useful in the prevention and treatment of stroke and other cardiovascular disorders, like myocardial infarction.

IT **171714-84-4**, LU 135252 **177036-94-1**, BSF208075 **531491-64-2**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method and composition for potentiating antipyretic action of nonopioid analgesic)

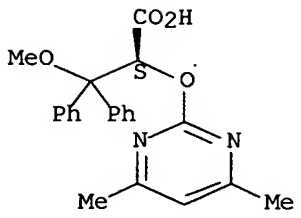
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 177036-94-1 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethyl-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

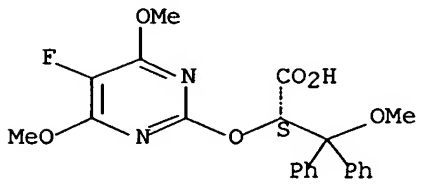
Absolute stereochemistry.



RN 531491-64-2 CAPLUS

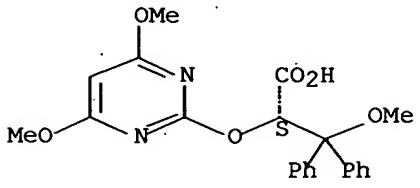
CN Benzenepropanoic acid, α-[(5-fluoro-4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L11 ANSWER 33 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2003:1000017 CAPLUS Full-text
DN 141:99337
TI Development and evaluation of an experimental model for investigating the pathogenesis and therapeutic strategies of acute liver failure
AU Skawran, S.; Palmes, D.; Budny, T.; Bahde, R.; Stratmann, U.; Spiegel, H. U.
CS Department of Surgery, Muenster University Hospital, Muenster, 48149, Germany
SO Transplantation Proceedings (2003), 35(8), 3142-3146
CODEN: TRPPA8; ISSN: 0041-1345
PB Elsevier Science Inc.
DT Journal
LA English
AB Because of the various etiologies of acute liver failure (ALF) a clin. relevant model must fulfill four criteria-reversibility, reproducibility, ALF-induced death, and a sufficient time interval for diagnosis and therapy between induction and death. In this study an exptl. model was evaluated for these criteria. A total of 49 rats were randomized into seven groups: First, a pilot study was performed regarding the survival rate after different treatments: In group I, animals underwent a 70% liver resection. In group II, 70% liver resection was combined with ascending doses of postoperative endotoxin administration up to 400 μg/kg (group IIc). In group III, animals only underwent liver mobilization. In group IV, ALF was induced according to the protocol of group IIc, but with addnl. treatment of an endothelin-A-receptor (ETAR) antagonist. Animals in group V received only 400 μg endotoxin. After induction of ALF, all animals died within the first day, showing significantly elevated bilirubin and ammonium levels and severe damage to hepatocellular integrity. Application of the ETAR antagonist resulted in the survival of 6/7 animals until the 14th day; the biochem. and histomorphol. changes were reversible. All other animals survived to the 14th day. A clin. relevant model of ALF in rats can be created by the combination of 70% liver resection and endotoxin application to produce an inflammatory component.
IT **171714-84-4**, Darusentan
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(development and evaluation of exptl. model for investigating pathogenesis and therapeutic strategies of acute liver failure in rats)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

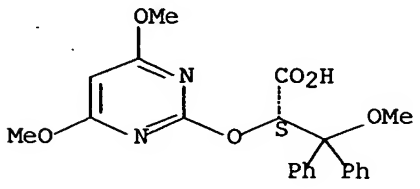
Absolute stereochemistry.



RE.CNT 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 34 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2003:973965 CAPLUS Full-text
DN 140:314747
TI Meta-analysis of the effects of endothelin receptor blockade on survival in experimental heart failure
AU Lee, Douglas S.; Nguyen, Quang T.; Lapointe, Nathalie; Austin, Peter C.; Ohlsson, Arne; Tu, Jack V.; Stewart, Duncan J.; Rouleau, Jean L.
CS Departments of Medicine, University of Toronto, Toronto, ON, Can.
SO Journal of Cardiac Failure (2003), 9(5), 368-374
CODEN: JCFAF9; ISSN: 1071-9164
PB Churchill Livingstone
DT Journal
LA English
AB Although an initial study of endothelin receptor blockade reported pos. findings, subsequent expts. and clin. trials in humans found little or no benefit. We applied meta-analytic methods to assess the methodol. rigor of preclin. studies of endothelia blockade and to quant. evaluate the totality of evidence regarding the effect of endothelia receptor blockers in exptl. heart failure. A total of 396 animals were assigned to control and 594 were assigned to exptl. therapy in the pooled anal. Of the 9 studies identified, no study reported a priori sample size justification. Although there was a tendency to increased mortality with early administration (relative risk 1.39, P = .15) and decreased mortality with late administration (relative risk 0.85, P = .6), in the overall anal., there was no significant evidence of benefit or harm (relative risk 1.03, P = .9). Studies with a small sample size had estimated effects that tended to deviate further from the pooled estimate of all studies. Consideration of mortality effects in the totality of studies revealed no significant effect of endothelin antagonists in animal models of exptl. heart failure. Given the potential for between-study variability, reliance on studies with small sample size may lead to unrealistic expectations when extrapolating preclin. exptl. results to future research.
IT **171714-84-4**, LU135252
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of endothelin receptor blockade on survival in exptl. heart failure)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

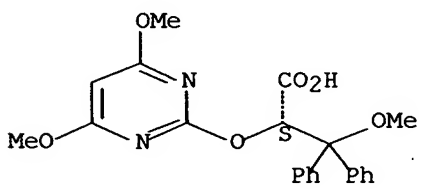
Absolute stereochemistry.



RE.CNT 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 35 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2003:945229 CAPLUS Full-text
DN 140:350268
TI Renal damage is not improved by blockade of endothelin receptors in primary renin-dependent hypertension
AU Rothermund, Lars; Kossmehl, Peter; Neumayer, Hans-H.; Paul, Martin; Kreutz, Reinhold
CS Institut fuer Klinische Pharmakologie und Toxikologie, Berlin, Germany
SO Journal of Hypertension (2003), 21(12), 2389-2397
CODEN: JOHYD3; ISSN: 0263-6352
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB OBJECTIVE: Secondary activation of the renin-angiotensin system plays a major role in the progression of chronic nephropathies, and blockade of endothelin (ET) receptors has been shown to confer nephroprotection in exptl. models of proteinuric renal disease. The authors tested the nephroprotective potential of selective endothelin A receptor (ETA) and nonselective ETA and endothelin B (ETA/B) receptor blockade in the TGR(mRen2)27 transgenic rat model with renin-dependent hypertension (Ren2). DESIGN: Ren2 animals were treated between 10 and 30 wk of age with the selective ETA receptor antagonist darusentan (Ren2-ETA) and the ETA/B receptor antagonist Lu420627 (Ren2-ETA/B), and compared with transgene neg. Sprague-Dawley (SD) controls. Since the elevated systolic blood pressure in Ren2 was not affected in either Ren2-ETA or Ren2-ETA/ETB, an addnl. Ren-2 group was treated with a nonantihypertensive dose of the angiotensin II type 1 receptor blocker eprosartan (Ren2-AT1). RESULTS: During the 20-wk observation period 35% of untreated Ren2, 30% of Ren2-ETA/B, 50% of Ren2-ETA, and 83% of Ren2-AT1 animals survived compared with 100% of SD rats. Renal endothelin-1 mRNA expression and proteinuria (4.1-fold) were significantly elevated in Ren2 compared with SD rats ($P < 0.05$, resp.). Proteinuria was normalized to SD control levels in Ren2-AT1 ($P < 0.05$) but increased further in Ren2-ETA (7.7-fold) and Ren2-ETA/B (15-fold) ($P < 0.05$, resp.). Glomerulosclerosis, tubulointerstitial damage and renal osteopontin mRNA expression were reduced in Ren2-AT1 ($P < 0.05$, resp.) but remained unchanged or increased further in Ren2-ETA and Ren2-ETA/B compared with Ren2. CONCLUSION: ET receptor blockade fails to improve renal damage and mortality in primary renin-dependent hypertension.
IT **171714-84-4**, Darusentan
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(renal damage is not improved by blockade of endothelin receptors in primary renin-dependent hypertension)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

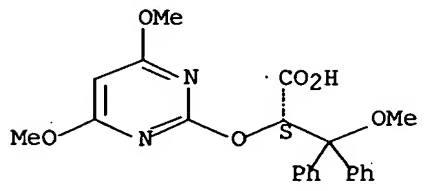
Absolute stereochemistry.



RE.CNT 67 THERE ARE 67 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 36 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2003:882000 CAPLUS Full-text
DN 140:417583
TI Effect of Endothelin Blockade on Early Cardiovascular Remodeling in the One-Clip-Two-Kidney Hypertension of the Rat
AU Saam, Tobias; Ehmke, Heimo; Haas, Christian; Ritz, Eberhard; Amann, Kerstin
CS Department of Nephrology, University of Heidelberg, Germany
SO Kidney & Blood Pressure Research (2003), 26(5-6), 325-332
CODEN: KBPRFC; ISSN: 1420-4096
PB S. Karger AG
DT Journal
LA English
AB In models of hypertension and of renal failure, pharmacol. blockade of the ETA receptor has been shown to cause some inconsistent lowering of blood pressure (BP) and lesser left ventricular hypertrophy (LVH). The effects of ETA receptor blockade (ETA-RB) on vascular remodeling and their potential relation to BP lowering, have not been clarified. The exptl. study in male Sprague-Dawley rats was designed to compare four exptl. groups: (1) sham-operated controls (sham); (2) untreated rats with one-clip-two-kidney (1C-2K) renovascular hypertension; (3) 1C-2K rats treated with the ACE inhibitor (ACE-i) trandolapril (0.3 mg/kg b.w./day), and (4) 1C-2K rats treated with the ETA-RB LU-135252 (50 mg/kg b.w./day). BP was measured weekly by tail plethysmog. After 3 wk, animals were sacrificed and cardiac, aortic and mesenteric artery morphol. was evaluated using morphometric and stereol. techniques. Systolic BP was significantly higher in 1C-2K rats compared to sham. BP was not significantly affected by ETA-RB, but was significantly lowered by the ACE-i. Despite no significant change in BP, ETA-RB treatment led to a significantly less volume d. of the cardiac interstitium (sham 1.40 ± 0.18, 1C-2K 2.66 ± 0.56, 1C-2K + ACE-i 1.88 ± 0.38, 1C-2K + ETA-RB 2.15 ± 0.37%). In contrast, ETA-RB had no significant effect on left ventricular/body weight ratio (sham 2.85 ± 0.26, 1C-2K 2.96 ± 0.33, 1C-2K + ACE-i 2.54 ± 0.22 and 1C-2K + ETA-RB 3.15 ± 0.44 mg/g) or on wall thickness of intramyocardial arteries. The ETA-RB LU-135252 ameliorated the development of myocardial fibrosis in a short-term hyperreninemic normal salt model of exptl. hypertension nearly as effectively as an ACE-i. This effect of LU-135252 is independent of systemic BP. In contrast to findings in other models, ETA receptor blockade had no significant effect on LVH or vascular remodeling. Only the ACE-i but not the ETA-RB prevented structural changes of small intramyocardial arteries and of the aorta.
IT **171714-84-4**, Darusentan
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effect of endothelin blockade vs. ACE inhibitor on early cardiovascular remodeling in one-clip-two-kidney hypertension of rat)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

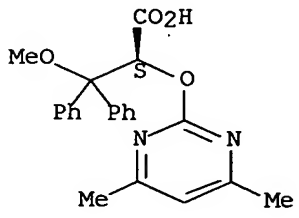
Absolute stereochemistry.



RE.CNT 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 37 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2003:770833 CAPLUS Full-text
DN 140:264086
TI Influence of a selective endothelinA receptor antagonist on the quantitative mRNA expression and the immunohistochemistry of vasoactive mediators after pancreas transplantation
AU Gabel, G.; Uhlmann, D.; Teupser, D.; Armann, B.; Tannapfel, A.; Ludwig, S.; Escher, E.; Pietsch, U.; Fiedler, G. M.; Hauss, J.; Witzigmann, H.
CS Department of Abdominal Transplantation and Vascular Surgery, University of Leipzig, Leipzig, Germany
SO Transplantation Proceedings (2003), 35(6), 2137-2138
CODEN: TRPPA8; ISSN: 0041-1345
PB Elsevier Science Inc.
DT Journal
LA English
AB The gene expression and synthesis of prepro-endothelin-1, endothelinA receptor (ETA) and proinflammatory cytokines IL-1β and IL-6 were examined In addition, it was also studied whether administration of a selective endothelinA receptor antagonist has any effect on the quant. mRNA expression and the immunohistochem. of these mediators. Results showed that in the pig pancreas transplantation model, the ETA-RA BSF 208075 diminished the increase of ET-1 expression in the graft tissue. The high ET-1 mRNA expression and pos. immunostaining in the control group supports the hypothesis that ET-1 could play an important role in the pathogenesis of I/R injury. The accumulation of ET-1 in the plasma of the treated animals may reflect the effectiveness of the receptor blockade by the ETA-RA. The application of a selective ATA receptor antagonist leads to significantly reduced mRNA expression and synthesis of ET-1 and an increased expression of ETA mRNA in the porcine pancreas graft.
IT **177036-94-1**, BSF 208075
RL: PAC (Pharmacological activity); BIOL (Biological study)
(effect of a selective endothelinA receptor antagonist on quant. mRNA expression and immunohistochem. of vasoactive mediators after pancreas transplantation)
RN 177036-94-1 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethyl-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

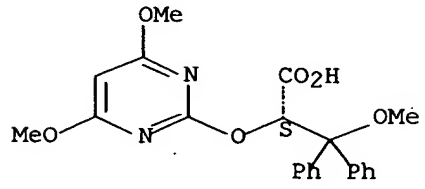
Absolute stereochemistry.



RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 38 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2003:710690 CAPLUS Full-text
DN 140:210246
TI Renal Damage in the SHR/N-cp Type 2 Diabetes Model: Comparison of an Angiotensin-Converting Enzyme Inhibitor and Endothelin Receptor Blocker
AU Gross, Marie-Luise; Ritz, Eberhard; Schoof, Arne; Helmke, Burkhard; Parkman, Amy; Tulp, Orien; Muenter, Klaus; Amann, Kerstin
CS Department of Pathology, University of Heidelberg, Heidelberg, Germany
SO Laboratory Investigation (2003), 83(9), 1267-1277
CODEN: LAINAW; ISSN: 0023-6837
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB The pathomechanisms that cause renal damage in diabetes have not been completely clarified. Treatment with angiotensin-converting enzyme inhibitors (ACE-i) is highly effective but fails to completely prevent end-stage renal disease. The effects of ETA-receptor blockers (ETA-RB) on renal damage are controversial and have rarely been investigated in type 2 diabetes. The authors compared the influence of the selective ETA-RB LU135252 and the ACE-i Trandolapril on renal structure in the SHR/N-cp rat model of type 2 diabetes. Three-month-old male SHR/N-cp rats were left untreated or received daily either Trandolapril or LU135252. The experiment was terminated after 6 mo. The glomerulosclerosis index; tubulointerstitial damage index; and glomerular geometry, glomerular cell number, and capillary d. were investigated. Proliferating cell nuclear antigen and desmin expression of podocytes, renal mRNA expression of endothelin (ET-1) and transforming growth factor-β, blood pressure, and urine albumin excretion were measured. The glomerulosclerosis index was significantly higher in untreated diabetic animals than in the groups that were treated with ACE-i and ETA-RB. There were analogous changes in tubulointerstitial damage index. Treatment with either substance comparably lowered urinary albumin excretion in diabetic SHR/N-cp. Podocyte and endothelial cell nos. per glomerulus decreased in untreated diabetic animals; this was prevented by the ACE-i but not by the ETA-RB. Glomerular capillary length d. was lower in SHR/N-cp, and this was normalized by ACE-i only. Increased expression of desmin and proliferating cell nuclear antigen expression of podocytes in the SHR/N-cp was abrogated by ACE-i but not by ETA-RB. Treatment with ACE-i or ETA-receptor antagonist resulted in less structural and functional alterations, but the ETA-RB was inferior to the ACE-i. This is particularly the case for podocyte changes pointing to angiotensin II-dependent pathomechanisms.
IT **171714-84-4**, LU135252
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(renal damage in SHR/N-cp type 2 diabetes model in relation to effects of angiotensin-converting enzyme inhibitor vs. endothelin receptor blocker)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

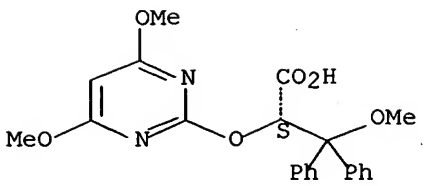
Absolute stereochemistry.



RE.CNT 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD

L11 ANSWER 39 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2003:498040 CAPLUS Full-text
DN 140:104789
TI ACE-inhibitors but not endothelin receptor blockers prevent podocyte loss in early diabetic nephropathy
AU Gross, M.-L.; El-Shakmak, A.; Szabo, A.; Koch, A.; Kuhlmann, A.; Muenter, K.; Ritz, E.; Amann, K.
CS Department of Pathology, University of Heidelberg, Heidelberg, 69120, Germany
SO Diabetologia (2003), 46(6), 856-868
CODEN: DBTGAJ; ISSN: 0012-186X
PB Springer-Verlag
DT Journal
LA English
AB It was the aim of our study to investigate the influence of a selective ET-A receptor antagonist LU 135252 alone and in combination with the ACE-inhibitor, trandolapril on podocyte number and morphol. in streptozotocin diabetic rats. Male Sprague-Dawley rats were injected with 65 mg streptozotocin i.v. and subsequently developed diabetes. Animals were left untreated or received daily either trandolapril (0.3 mg/kg body weight), LU 135252 (50 mg/kg body weight) or a combination of both. After 6 mo the experiment was terminated. Glomerular geometry and cellularity were assessed by stereol. techniques. Protein expression of TGF-β, ET-1, PDGF-AB, fibronectin, desmin and α-smooth muscle cell actin was investigated by immunohistochem. The mean number of podocytes per glomerulus was lower (86±17 vs. 138±25; $p<0.05$) and mean podocyte volume was higher in untreated diabetic animals than in non-diabetic controls. Only ACE-i alone and in combination, but not ETA-RB alone prevented loss of podocytes and podocyte hypertrophy. In diabetic rats, increased nos. of PCNA pos. and p27kip1 pos. cells (mainly podocytes) were reduced by all treatments, but only ACE-i decreased nos. of desmin pos. podocytes and tubulointerstitial expression of TGF-β. Albuminuria was increased in untreated diabetes and was prevented only by ACE-i and combination treatment. Podocyte hypertrophy and degeneration is an early event in diabetic nephropathy leading to a loss of podocytes. Treatment with an ACE-i, but not with an ETA-RB, prevented the development of albuminuria as well as damage and loss of podocytes. The well known anti-proteinuric effect of ACE-i is presumably due at least in part to conservation of podocyte structure. Increased plasma endothelin-1 (ET-1) concns. and urine excretion of ET-1 have been documented in patients with diabetes and proteinuria. It has been shown that exptl. diabetes mellitus increases renal ET-1 gene transcription. To assess the relevance of the ET-system in the pathogenesis of renal structural changes in the model of the STZ-induced diabetic rat we compared the effect of an ETA-receptor specific antagonist with the well known beneficial effect of an ACE-i, especially on podocyte cell number and morphol.
IT **171714-84-4**, LU 135252
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(influence of ET-A receptor antagonist LU 135252 alone or in combination with ACE-inhibitor trandolapril on podocyte number in diabetic nephropathy)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

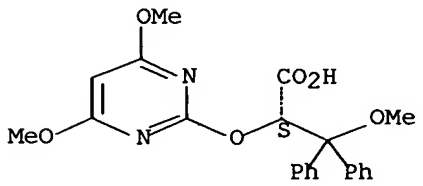
Absolute stereochemistry.



RE.CNT 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 40 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2003:452960 CAPLUS Full-text
DN 139:345625
TI Enalaprilat, losartan and LU 135252 in coronary blood flow regulation
AU Rigol, M.; Heras, M.; Solanes, N.; Epelde, F.; Roig, E.; Perez-Villa, F.; Roque, M.; Sanz, G.
CS IDIBAPS, Hospital Clinic, Institut de Malalties Cardiovasculars, Barcelona, Spain
SO European Journal of Clinical Investigation (2003), 33(5), 363-369
CODEN: EJCIB8; ISSN: 0014-2972
PB Blackwell Publishing Ltd.
DT Journal
LA English
AB Background: High plasma levels of angiotensin II are found in several pathologies such as hypertension, heart failure and myocardial infarction. The effect of high concns. of angiotensin II on coronary circulation is not well defined. The aim of the present study was to assess coronary blood flow regulation during tachycardia in the presence of elevated coronary plasma levels of angiotensin II, and the changes induced by ACE inhibition and blockade of angiotensin II and endothelin-A receptors. Design: Left anterior coronary artery was catheterized in 38 pigs to infuse the study drugs. Saline was infused for 15 min. Then, the first atrial pacing was performed. The pigs were distributed to: Group 1 (n = 7) angiotensin II; Group 2 enalaprilat + angiotensin II; Group 3 the bradykinin B2 antagonist HOE 140 + enalaprilat + angiotensin II; Group 4 losartan + angiotensin II; and Group 5 endothelin-A receptor antagonist LU 135252 + angiotensin II. After giving these infusions, a second pacing was repeated. Results: The increase in coronary blood flow induced by pacing with angiotensin II was reduced from 181% to 116%. Enalaprilat, losartan and LU 135252 restored the capacity of coronary blood flow to increase during pacing (151%, 162% and 161%, resp.), while HOE 140 abolished the effect of enalaprilat. Conclusions: Moderately elevated coronary concns. of angiotensin II reduced coronary blood flow during pacing. Enalaprilat, losartan and LU 135252 restored the hyperemic coronary flow to similar values observed with saline. The beneficial effect of ACE inhibition is mediated through an increase in bradykinin.
IT **171714-84-4**, LU 135252
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); BIOL (Biological study)
(enalaprilat and losartan and LU 135252 effect on coronary blood flow regulation during angiotensin II elevation)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

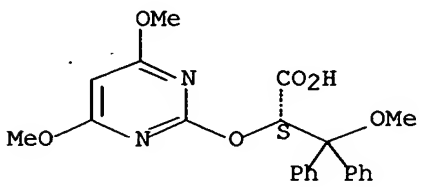
Absolute stereochemistry.



RE.CNT 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 41 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2003:445078 CAPLUS Full-text
DN 139:317128
TI Effects of the Endothelin A Receptor Antagonist Darusentan on Blood Pressure and Vascular Contractility in Type 2 Diabetic Goto-Kakizaki Rats
AU Witte, Klaus; Reitenbach, Ina; Stolpe, Kerstin; Schilling, Lothar; Kirchengast, Michael; Lemmer, Bjoern
CS Institute of Pharmacology and Toxicology and Department of Neurosurgical Research, University of Heidelberg, Germany
SO Journal of Cardiovascular Pharmacology (2003), 41(6), 890-896
CODEN: JCPCDT; ISSN: 0160-2446
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB The present study evaluated the effects of long-term treatment with the endothelin A (ETA) receptor antagonist darusentan (LU135252) on blood pressure (BP) and vascular target-organ damage in spontaneously type 2 diabetic Goto-Kakizaki (GK) rats. BP was monitored by radiotelemetry in untreated and darusentan-treated GK rats from 10-24 wk of age. Relaxation of mesenteric artery segments by acetylcholine (ACh) and sodium nitroprusside (SNP) was measured to assess endothelium-dependent and -independent vasorelaxation. Aortic soluble guanylyl cyclase (sGC) activity was studied in vitro after stimulation by the nitric oxide (NO) donor diethylamine-NONOate. Untreated GKs were mildly hypertensive and showed a blunted vascular relaxation by ACh and SNP and a reduction in NO-stimulated sGC activity in comparison with Wistar control rats. Darusentan led to a small but sustained reduction in 24-h BP but did not restore the endothelium-dependent vasorelaxation nor the NO-stimulated cGMP formation in GK rats. The present findings suggest that an activated endothelin pathway may contribute to elevated BP but is not involved in vascular dysfunction in this animal model of type II diabetes.
IT **171714-84-4**, Darusentan
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of endothelin A receptor antagonist darusentan on blood pressure and vascular contractility in type 2 diabetic Goto-Kakizaki rats)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 42 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2003:414077 CAPLUS Full-text
DN 139:957
TI Method and composition using an endothelin antagonist for potentiating an opiate analgesic
IN Gulati, Anil
PA USA
SO U.S. Pat. Appl. Publ., 55 pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2003100507	A1	20030529	US 2002-301449	20021121
	CA 2464768	AA	20030605	CA 2002-2464768	20021122
	WO 2003045434	A2	20030605	WO 2002-US37461	20021122
	WO 2003045434	A3	20030925		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	AU 2002348224	A1	20030610	AU 2002-348224	20021122
	EP 1448233	A2	20040825	EP 2002-782353	20021122
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
	BR 2002014481	A	20040914	BR 2002-14481	20021122
	JP 2005513033	T2	20050512	JP 2003-546935	20021122
	CN 1646166	A	20050727	CN 2002-823570	20021122
	ZA 2004003162	A	20050126	ZA 2004-3162	20040426
	NO 2004002612	A	20040622	NO 2004-2612	20040622
PRAI	US 2001-333599P	P	20011127		
	WO 2002-US37461	W	20021122		

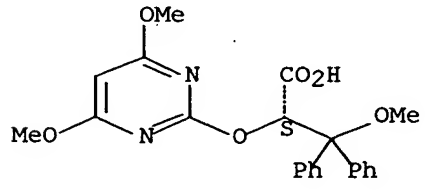
AB A composition and methods for treating pain and reducing or reversing tolerance to opiate analgesics are disclosed. The composition and methods use an opiate analgesic and an endothelin antagonist as active agents to treat pain in mammals, including humans.

IT **171714-84-4 177036-94-1**, BSF208075 **531491-64-2**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(endothelin antagonist for potentiation of opiate analgesic)

RN 171714-84-4 CAPLUS

CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

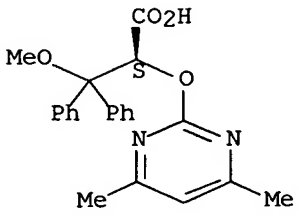
Absolute stereochemistry.



RN 177036-94-1 CAPLUS

CN Benzenepropanoic acid, α-[(4,6-dimethyl-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

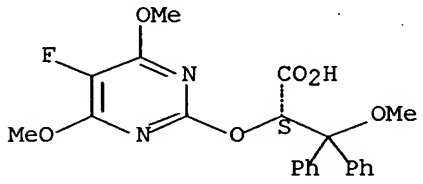
Absolute stereochemistry.



RN 531491-64-2 CAPLUS

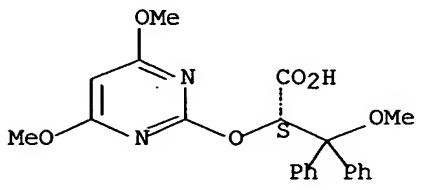
CN Benzenepropanoic acid, α-[(5-fluoro-4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L11 ANSWER 43 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2003:365034 CAPLUS Full-text
DN 139:207421
TI Nephroprotective effects of the endothelin ETA receptor antagonist darusentan in salt-sensitive genetic hypertension
AU Rothermund, Lars; Traupe, Tobias; Dieterich, Maike; Kossmehl, Peter; Yagil, Chana; Yagil, Yoram; Kreutz, Reinhold
CS Institut fur Klinische Pharmakologie und Toxikologie, Benjamin Franklin Hospital, Freie Universitat Berlin, Berlin, 12200, Germany
SO European Journal of Pharmacology (2003), 468(3), 209-216
CODEN: EJPHAZ; ISSN: 0014-2999
PB Elsevier Science B.V.
DT Journal
LA English
AB We tested the effect of selective endothelin ETA receptor blockade on the development renal damage in the Sabra rat model of genetic salt-sensitivity. Animals from the salt-sensitive (SBH/y) and salt-resistant strains (SBN/y) were either salt-loaded with deoxycorticosterone acetate and salt (DOCA) or fed a normal diet. Addnl. salt-loaded groups were also treated with the selective ETA antagonist darusentan (DA). Salt-loading in SBH/y increased systolic blood pressure by 75 mm Hg and urinary albumin excretion 23-fold (P<0.0001). Darusentan attenuated the rise of systolic blood pressure (50%) and urinary albumin excretion (63%, P<0.01, resp.). Salt-loading in SBH/y was associated with significant increased osteopontin mRNA expression as well as glomerulosclerosis and tubulointerstitial damage in the kidney (P<0.05, resp.). This was either significantly reduced or normalized by darusentan (P<0.05, resp.). Thus, darusentan confers a significant renal protection in the Sabra model of salt-sensitive hypertension.
IT **171714-84-4**, Darusentan
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nephroprotective effects of endothelin ETA receptor antagonist darusentan in genetic hypertension)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

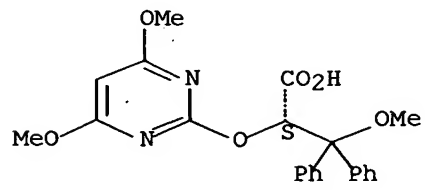
Absolute stereochemistry.



RE.CNT 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 44 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2003:326251 CAPLUS Full-text
DN 139:332728
TI Trandolapril and endothelin antagonist LU-135252 in the treatment of the fructose-induced hypertensive, hyperinsulinemic, hypertriglyceridemic rat
AU Ezra-Nimni, Orit; Ezra, David; Peleg, Edna; Munter, Klaus; Rosenthal, Talma
CS Chorley Institute for Hypertension Research, Chaim Sheba Medical Center, Tel Hashomer, Israel
SO American Journal of Hypertension (2003), 16(4), 324-328
CODEN: AJHYE6; ISSN: 0895-7061
PB Elsevier Science Inc.
DT Journal
LA English
AB Background: In view of the demonstrated interaction between endothelin and the renin-angiotensin system, the antihypertensive effect of combined therapy with an endothelin antagonist LU-135252 and the angiotensin converting enzyme inhibitor trandolapril, was studied in fructose-induced hypertensive, hyperinsulinemic, hypertriglyceridemic male Sprague-Dawley rats. Methods: Forty animals were fed a fructose-enriched diet (Tekled, Harlan) for 5 wk, as follows: group A, fructose only; group B, trandolapril 0.1 mg/kg/day added during the last 2 wk; group C, LU-135252 100 mg/kg/day added during the last 2 wk; group D, both trandolapril and LU-135252 added the last 2 wk. Systolic blood pressure (BP) was measured weekly in conscious rats by the indirect tail-cuff method. Blood samples from a retro-orbital sinus puncture were taken at the beginning of the experiment and after 3 and 5 wk and examined for insulin and triglyceride concns. Results: Systolic BP decreased in group B (trandolapril) from 148.8 at 3 wk to 138.3 mm Hg after 5 wk; in group C (endothelin antagonist) from 155.1 to 142.5 mm Hg; and in group D (combination) from 154.6 to 121.2 mm Hg. Triglyceride levels decreased only in the combined trandolapril/endothelin antagonist group from 167.6 in the third week to 134.9 mg/dL after 5 wk. Insulin levels decreased only on combination therapy from 7.4 to 5.3 ng/mL during the same period. The BP decrease was additive compared with the resp. individual substances. Conclusions: The trandolapril/endothelin antagonist combination appears to offer a rational antihypertensive combination that is superior to that of either drug alone. This finding applies to the specific rat model studied in which BP, insulin, and triglycerides were increased by fructose diet.
IT **171714-84-4**, LU-135252
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(trandolapril and endothelin antagonist LU-135252 treatment of fructose-induced hypertensive and hyperinsulinemic and hypertriglyceridemic rats)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

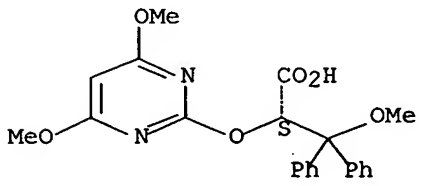
Absolute stereochemistry.



RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

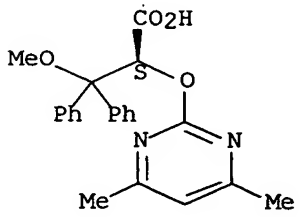
L11 ANSWER 45 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2003:305390 CAPLUS Full-text
DN 138:331480
TI Endothelin 1 type A receptor antagonism prevents vascular dysfunction and hypertension induced by 11β-hydroxysteroid dehydrogenase inhibition. Role of nitric oxide. [Erratum to document cited in CA136:272903]
AU Ruschitzka, Frank; Quaschning, Thomas; Noll, Georg; de Gottardi, Andrea; Rossier, Michel F.; Enseleit, Frank; Hurlimann, David; Luscher, Thomas F.; Shaw, Sidney G.
CS Cardiovascular Research and Institute of Physiology, University Hospital Zurich, Zurich, Switz.
SO Circulation (2001), 104(10), 1208
CODEN: CIRCAZ; ISSN: 0009-7322
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB The columns in Figure 1A were mislabeled; the corrected figure and legend are given. Figure 1B was correct as printed. In the Results section, the first sentence should read as follows: "(THB + allo-THB)/THA ratio as an index of 11β-HSD activity was increased, indicating decreased 11β-HSD activity in GA-treated rats ($P < 0.05$ vs. controls; Figure 1A).".
IT **171714-84-4**, LU135252
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(endothelin 1 type A receptor antagonism prevents vascular dysfunction and hypertension induced by 11β-hydroxysteroid dehydrogenase inhibition and role of nitric oxide (Erratum))
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L11 ANSWER 46 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2003:250727 CAPLUS Full-text
DN 139:317212
TI Cerebrovascular Characterization of the Novel Nonpeptide Endothelin-A Receptor Antagonist LU 208075
AU Vatter, Hartmut; Zimmermann, Michael; Weyrauch, Edda; Lange, Bettina N.; Setzer, Matthias; Raabe, Andreas; Seifert, Volker
CS Dep. of neurosurgery, Johann Wolfgang Goethe-Univ., Frankfurt, D-60528, Germany
SO Clinical Neuropharmacology (2003), 26(2), 73-83
CODEN: CLNEDB; ISSN: 0362-5664
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB Enhanced cerebrovascular resistance under pathol. conditions, like cerebral vasospasm after subarachnoid hemorrhage, seems to be caused by the vasocontractile effect of endothelin-1 (ET-1). Therefore, the effect of the novel and ET(A) receptor selective antagonist LU 208075 was characterized by the contraction and relaxation induced by ET-1 and bigET-1 on rat basilar artery. Basilar artery ring segments with (E+) and without (E-) functionally intact endothelium were prepared to measure the isometric force. Concentration-effect curves were constructed by cumulative application of ET-1 or bigET-1 in the presence of LU 208075 (10-7M, 10-6M, and 10-5M). The effect of LU 208075 was determined by the pA2 value. The contraction by ET-1 and bigET-1 was inhibited by LU 208075 in a dose-dependent manner. The pA2 values for ET-1 and for bigET-1 were 6.51±0.39 (E+) and 6.67±0.43 (E-), and 7.03±0.32 (E+) and 7.24±0.31 (E-) resp. The E(max) values for bigET-1 but not for ET-1 were reduced significantly in the presence of LU 208075. A significant relaxation by ET-1 or bigET-1 was observed only in the presence of LU 208075. This relaxation was inhibited by LU 208075 in higher concns., with pA2 values of 5.68±0.05 (ET-1) and 5.50±0.39 (bigET-1). The current data correlate with a competitive inhibition of ET(A) receptor-mediated contraction and relaxation, caused by ET(B) receptor activation on cerebral vessels by LU 208075. The selectivity for the ET(A) receptor was approx. sevenfold. Furthermore, the results may suggest an inhibition of the functional ET-converting enzyme activity by LU 208075.
IT **177036-94-1**, LU 208075
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cerebrovascular characterization of novel nonpeptide endothelin-A receptor antagonist LU 208075)
RN 177036-94-1 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethyl-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

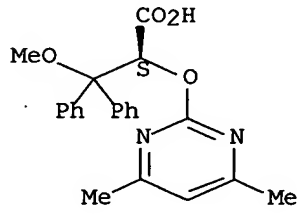
Absolute stereochemistry.



RE.CNT 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 47 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2003:145024 CAPLUS Full-text
DN 138:296953
TI Ambrisentan Myogen
AU Billman, George E.
CS Department of Physiology and Cell Biology, The Ohio State University, Columbus, OH, 43210-1218, USA
SO Current Opinion in Investigational Drugs (PharmaPress Ltd.) (2002), 3(10), 1483-1486
CODEN: COIDAZ; ISSN: 1472-4472
PB PharmaPress Ltd.
DT Journal; General Review
LA English
AB A review. Ambrisentan (LU-208075, BSF-208075) and LU-302146 (BSF-302146) are being developed by Myogen, under license from Abbott (formerly BASF Pharma), for the potential treatment of post-ischemic acute renal failure and cardiovascular disease [343902], [394232], [398274]. By August 2001, ambrisentan had entered phase II trials for chronic heart failure, hypertension, kidney failure and pulmonary hypertension [420580].
IT **177036-94-1**, Ambrisentan
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antihypertensive ambrisentan for treatment of cardiovascular disease patients)
RN 177036-94-1 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethyl-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

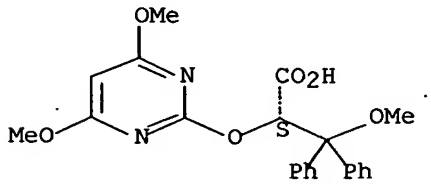
Absolute stereochemistry.



RE.CNT 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 48 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2003:107039 CAPLUS Full-text
DN 138:349004
TI Erythropoietin-induced excessive erythrocytosis activates the tissue endothelin system in mice
AU Quaschning, Thomas; Ruschitzka, Frank; Stallmach, Thomas; Shaw, Sidney; Morawietz, Henning; Goettsch, Winfried; Hermann, Matthias; Slowinski, Torsten; Theuring, Franz
CS Cardiol. and Cardiovascular Res. and Inst. of Physiol., Univ. of Zuerich, Zurich, CH-8057, Switz.
SO FASEB Journal (2003), 17(2), 259-261, 10.1096/fj.02-0296fje
CODEN: FAJOEC; ISSN: 0892-6638
PB Federation of American Societies for Experimental Biology
DT Journal
LA English
AB The endothelium controls blood flow and pressure by releasing several vasoactive factors, among them the vasodilator nitric oxide (NO) and the potent vasoconstrictor endothelin-1 (ET-1). Although increased NO levels have been found in excessive erythrocytosis, little is known concerning ET-1 expression in this condition. Thus, the authors examined the endothelin system in transgenic mice that due to constitutive over-expression of erythropoietin (Epo) reached hematocrit levels of .apprx.80%. Surprisingly, despite generalized vasodilatation, polycythemic mice exhibited a two- to fivefold elevation in ET-1 mRNA levels in aorta, liver, heart, and kidney. In line with this, increased expression of ET-1 protein was detected in the pulmonary artery by immunohistochem. anal. Compared with their wild-type littermates, aortic rings of Epo transgenic animals exhibited a marked reduction in vascular reactivity to ET-1 and big ET-1, but this effect was abrogated upon preincubation with the NO synthase inhibitor N-nitro-L-arginine Me ester (L-NAME). Pretreatment of polycythemic mice with the ETA receptor antagonist darusentan for 3 wk significantly prolonged their survival upon acute exposure to L-NAME. Taken together, these results demonstrate for the first time that excessive erythrocytosis induces a marked activation of the tissue endothelin system that results in increased mortality upon blockade of NO-mediated vasodilatation. Because ETA antagonism prolonged survival after acute blockade of NO synthesis, endothelin may be regarded as a contributor to the adverse cardiovascular effects of erythrocytosis and may thus represent a new target in the treatment of cardiovascular disease associated with erythrocytosis.
IT **171714-84-4**, Darusentan
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(erythropoietin induced excessive erythrocytosis activates tissue endothelin system in mouse in relation to effect of darusentan)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

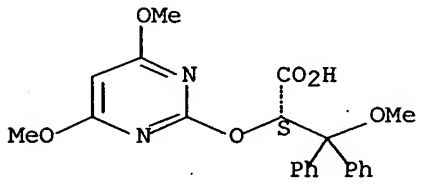
Absolute stereochemistry.



RE.CNT 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 49 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2003:52527 CAPLUS Full-text
DN 139:78391
TI Prediction of biological activity spectra for substances: evaluation on the diverse sets of drug-like structures
AU Stepanchikova, A. V.; Lagunin, A. A.; Filimonov, D. A.; Poroikov, V. V.
CS Institute of Biomedical Chemistry RAMS, Moscow, 119121, Russia
SO Current Medicinal Chemistry (2003), 10(3), 225-233
CODEN: CMCHE7; ISSN: 0929-8673
PB Bentham Science Publishers
DT Journal
LA English
AB The concept of Biol. Activity Spectrum served as a basis for developing PASS (Prediction of Activity Spectra for Substances) software product. PASS predicts simultaneously more than 780 pharmacol. effects and biochem. mechanisms based on the structural formula of a substance. It may be used for finding new targets (mechanisms) for known pharmaceuticals and for searching new biol. active substances. PASS prediction ability was evaluated by activity spectra prediction for 63 substances that are presented in the Mol. of the Month section of Prous Science, belong to different chemical classes and reveal various types of biol. activity. Mean accuracy of prediction turned out to be about 90%; therefore, it is reasonable to use PASS for finding and optimizing new lead compds. A web-site with a new internet version of PASS is introduced into practice in Dec. 2001. On the site, one can find a detailed description of the PASS approach as well as some examples of its applications, and estimate the quality of prediction by submitting structures of substances with known activities.
IT **171714-84-4**, Darusentan
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(biol. activity spectra evaluation of drug-like structures)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

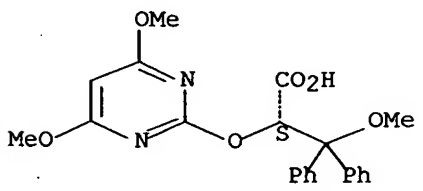
Absolute stereochemistry.



RE.CNT 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 50 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2002:854803 CAPLUS Full-text
DN 139:95075
TI Hemodynamic and Neurohumoral Effects of Selective Endothelin A (ETA) Receptor Blockade in Chronic Heart Failure. The heart failure ETA receptor blockade trial (HEAT)
AU Luescher, Thomas F.; Enseleit, Frank; Pacher, Richard; Mitrovic, Veselin; Schulze, Matthias R.; Willenbrock, Roland; Dietz, Rainer; Rousson, Valentin; Huerlimann, David; Philipp, Sebastian; Notter, Thomas; Noll, Georg; Ruschitzka, Frank
CS Cardiology, Cardiovascular Center, University Hospital, Zurich, CH-8091, Switz.
SO Circulation (2002), 106(21), 2666-2672
CODEN: CIRCAZ; ISSN: 0009-7322
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB Background- The endothelin (ET-1) system is activated in chronic heart failure (CHF). Whether, what type, and what degree of selective ET blockade is clin. beneficial is unknown. We investigated hemodynamic and neurohumoral effects of 3 wk of treatment with various dosages of the orally available ETA antagonist darusentan in addition to modern standard therapy in patients with CHF. Methods and Results- A total of 157 patients with CHF (present or recent NYHA class III of at least 3 mo duration), pulmonary capillary wedge pressure 12 mm Hg, and a cardiac index ≤2.6 L·min-1·m-2 were randomly assigned to double-blind treatment with placebo or darusentan (30, 100, or 300 mg/d) in addition to standard therapy. Short-term administration of darusentan increased the cardiac index, but this did not reach statistical significance compared with placebo. The increase in cardiac index was significantly more pronounced after 3 wk of treatment. Pulmonary capillary wedge pressure, pulmonary arterial pressure, pulmonary vascular resistance, and right atrial pressure remained unchanged. Heart rate, mean artery pressure, and plasma catecholamines remained unaltered, but systemic vascular resistance decreased significantly. Higher dosages were associated with a trend to more adverse events (including death), particularly early exacerbation of CHF without further benefit on hemodynamics compared with moderate dosages. Conclusions- This study demonstrates for the first time in a large patient population that 3 wk of selective ETA receptor blockade improves cardiac index in patients with CHF. However, long-term studies are needed to determine whether ETA blockade is beneficial in CHF.
IT **171714-84-4**, Darusentan
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); BIOL (Biological study)
(hemodynamic and neurohumoral effects of selective endothelin ETA receptor blockade in chronic heart failure)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

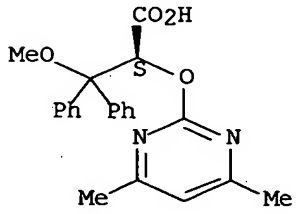
Absolute stereochemistry.



RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 51 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2002:829570 CAPLUS Full-text
DN 138:331455
TI Left But Not Right Cardiac Hypertrophy in Atrial Natriuretic Peptide Receptor-Deficient Mice Is Prevented by Angiotensin Type 1 Receptor Antagonist Losartan
AU Holtwick, Rita; Baba, Hideo A.; Ehler, Elisabeth; Risse, Dorothee; Vo, Melanie; Gehrmann, Joseph; Pierkes, Melanie; Kuhn, Michaela
CS Institute of Pharmacology and Toxicology, Universitatsklinikum Essen, Essen, Germany
SO Journal of Cardiovascular Pharmacology (2002), 40(5), 725-734
CODEN: JCPCDT; ISSN: 0160-2446
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB Mice with a genetic deletion of the atrial natriuretic peptide (ANP) receptor, guanylyl cyclase A (GC-A -/-), have chronic arterial hypertension and cardiac hypertrophy from the first day of life. To characterize the role of the angiotensin II and endothelin systems in the development of this cardiovascular phenotype, the effects of chronic treatment with either the angiotensin type I (AT) receptor antagonist losartan or the endothelin A receptor antagonist BSF208075 were tested. Losartan almost completely reversed systemic arterial hypertension and left ventricular hypertrophy of GC-A -/- mice. This was accompanied by a marked regression of the left ventricular mRNA expression of cardiac hypertrophy markers such as ANP and brain natriuretic peptide and a significant reduction of left ventricular and pulmonary interstitial collagen accumulation. BSF208075 had no effect on any of these cardiovascular parameters. Intriguingly, GC-A -/- mice also showed a very marked right ventricular hypertrophy, which was not reversed by losartan or BSF208075 treatment. Analyses of components of the renin-angiotensin system (RAS) revealed an inhibition of renal and systemic RAS contrasting with increased local left ventricular angiotensin II levels in GC-A -/- mice. Collectively, the results suggest that RAS plays a more important role than the endothelin system in the pathogenesis of arterial hypertension as well as left ventricular hypertrophy and fibrosis in GC-A gene-disrupted mice.1.
IT **177036-94-1**, BSF208075
RL: PAC (Pharmacological activity); BIOL (Biological study)
(left but not right cardiac hypertrophy in atrial natriuretic peptide receptor-deficient mice is prevented by angiotensin type 1 receptor antagonist losartan)
RN 177036-94-1 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethyl-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

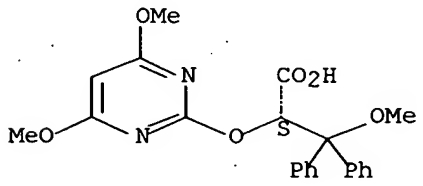
Absolute stereochemistry.



RE.CNT 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 52 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2002:826913 CAPLUS Full-text
DN 138:49321
TI Property-based design of GPCR-targeted library
AU Balakin, Konstantin V.; Tkachenko, Sergey E.; Lang, Stanley A.; Okun, Ilya; Ivashchenko, Andrey A.; Savchuk, Nikolay P.
CS Chemical Diversity Labs Inc., San Diego, CA, 92121, USA
SO Journal of Chemical Information and Computer Sciences (2002), 42(6), 1332-1342
CODEN: JCISD8; ISSN: 0095-2338
PB American Chemical Society
DT Journal
LA English
AB The design of a GPCR-targeted library, based on a scoring scheme for the classification of mols. into "GPCR-ligand-like" and "non-GPCR-ligand- like", is outlined. The methodol. is a valuable tool that can aid in the selection and prioritization of potential GPCR ligands for bioscreening from large collections of compds. It is based on the distillation of knowledge from large databases of GPCR and non-GPCR active agents. The method employed a set of descriptors for encoding the mol. structures and by training of a neural network for classifying the mols. The mol. requirements were profiled and validated by using available databases of GPCR- and non-GPCR-active agents. The method enables efficient qualification or disqualification of a mol. as a potential GPCR ligand and represents a useful tool for constraining the size of GPCR-targeted libraries that will help speed up the development of new GPCR-active drugs.
IT **171714-84-4**, Darusentan
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(property-based design of GPCR-targeted library)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

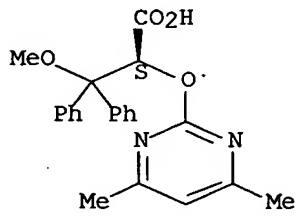
Absolute stereochemistry.



RE.CNT 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 53 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2002:816343 CAPLUS Full-text
DN 138:331450
TI Effect of the novel endothelin(A) receptor antagonist LU 208075 on contraction and relaxation of isolated rat basilar artery
AU Vatter, Hartmut; Zimmermann, Michael; Jung, Carla; Weyrauch, Edda; Lang, Josef; Seifert, Volker
CS Department of Neurosurgery, Johann Wolfgang Goethe-University, Frankfurt am Main, D-60528, Germany
SO Clinical Science (2002), 103(Suppl.), 408S-413S
CODEN: CSCIAE; ISSN: 0143-5221
PB Portland Press Ltd.
DT Journal
LA English
AB Increased levels of endothelin (ET)-1 and big ET-1 may be responsible for enhanced cerebroarterial resistance under pathol. conditions. Therefore, the effect of LU 208075, a novel ET(A)-selective receptor antagonist was determined The aim of the study was to investigate in vitro the inhibitory effect of LU 208075 on ET-1 and big ET-1 induced contraction and relaxation in rat basilar artery segments. Segments with (E+) and without (E-) endothelium were prepared for the measurement of isometric force. Concentration-effect curves (CECs) were constructed by cumulative application of ET-1 or big ET-1. The shift of the CECs in the presence of LU 208075 against the control curve was determined Relaxation was investigated on precontracted segments, calculated in percentage decrease of precontraction and compared by the pD2 and Emax. ET-1 and big ET-1 induced contraction was dose dependently inhibited by LU 208075. Shifts of the CECs in the presence of LU 208075 (10-6 M and 10-5 M) were for ET-1 (1) in E+ : 4.4 and 19.7; (2) in E- : 8.1 and 60.4 and for big ET-1 (3) in E+ : 10.8 and (4) in E- : 26.0, resp. LU 208075 (10-5 M) completely inhibited big ET-1-induced contraction. Relaxation by ET-1 or big ET-1 was only observed in the presence of LU 208075. CECs were shifted to the right by LU 208075 (10-5 M) by a factor of 24 (ET-1) and 4.5 (big ET-1). Emax values were 45% and 51% (ET-1; in the presence of 10-5 and 10-6 M LU 208075, resp.), and 56% and 49% (big ET-1; in the presence of 10-5 and 10-6 M LU 208075, resp.). The data suggests a competitive ET(A)-receptor inhibition by LU 208075. The enhanced inhibitory effect on big ET-1-induced contraction could indicate an addnl. inhibitory effect on endothelin-converting enzyme activity. The pronounced effect on E-vessels and the inhibition of relaxation may suggest an ET(B) receptor affinity.
IT **177036-94-1**, LU 208075
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); BIOL (Biological study)
(endothelin ETA receptor antagonist LU 208075 effect on endothelin-1 and big endothelin-1-induced contraction and relaxation of isolated rat basilar artery)
RN 177036-94-1 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethyl-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

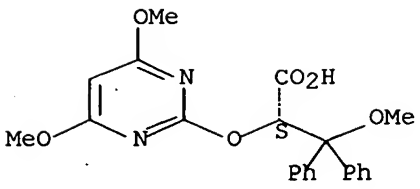
Absolute stereochemistry.



RE.CNT 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD

L11 ANSWER 54 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2002:816337 CAPLUS Full-text
DN 138:331449
TI Endothelin receptor A blockade reduces proteinuria and vascular hypertrophy in spontaneously hypertensive rats on high-salt diet in a blood-pressure-independent manner
AU Trenkner, Joerg; Priem, Friedrich; Bauer, Christian; Neumayer, Hans-Hellmut; Raschak, Manfred; Hocher, Berthold
CS Department of Nephrology, Humboldt University of Berlin, Berlin, 10098, Germany
SO Clinical Science (2002), 103(Suppl.), 385S-388S
CODEN: CSCIAE; ISSN: 0143-5221
PB Portland Press Ltd.
DT Journal
LA English
AB The renal endothelin (ET) system is involved in the pathogenesis of kidney fibrosis as well as blood pressure control by regulating tubular sodium excretion. Long-term effects of ETA receptor blockade on blood pressure and kidney function in spontaneously hypertensive rats (SHRs) on a high-salt diet are unknown. We treated SHRs on a 6% (weight/volume) NaCl sodium diet (SHR-S) for 48 wk with the ETA antagonist LU 135252 (whose selectivity for ETA is 150 times greater than for ETB) with 10, 30 and 100 mg/kg/day or placebo. The ETA antagonist had at no time-point any effect on blood pressure. Glomerular filtration rate was normal in SHR-S and not altered by LU 135252. However, urinary albumin excretion was markedly reduced by the ETA antagonist (SHR-S, 145 mg/day; SHR-S+ 10 mg/kg/day LU 135252, 33 mg/day; SHR-S+30 mg/kg/day LU 135252, 55 mg/day; and SHR-S+ 100 mg/kg/day LU 135252, 32 mg/day). Total urinary protein excretion was likewise significantly reduced by treatment with 10 mg/kg/day LU 135252 (SHR-S, 0.25 g/day; SHR-S+ 10 mg/kg/day LU 135252, 0.089 g/day). The higher dosages of LU 135252 showed only a trend towards reduction of total urinary protein excretion. Computer-aided image anal. after hematoxylin/eosin and periodic acid-Schiff staining revealed that treatment with 10 mg/kg/day LU 135252 significantly reduces the media/lm ratio of intrarenal arteries. Higher dosages of LU 135252 were less effective. Renal matrix protein synthesis in SHR-S was not altered by LU 135252. In conclusion, the renal ET system contributes in a blood-pressure-independent manner to the regulation of urinary protein excretion and renal vascular hypertrophy in SHR-S. Lower doses of the ETA antagonist were more effective, indicating that a potential addnl. blockade of the ETB receptor using higher doses of LU 135252 seems to oppose the beneficial effects of a sole ETA blockade. Urinary protein excretion is an independent risk factor of chronic renal failure, thus ETA antagonists might be a therapeutic tool to prevent proteinuria-induced chronic renal failure.
IT **171714-84-4**, LU 135252
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); BIOL (Biological study)
(endothelin ETA receptor blockade reduces proteinuria and vascular hypertrophy in spontaneously hypertensive rats on high-salt diet in blood-pressure-independent manner)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

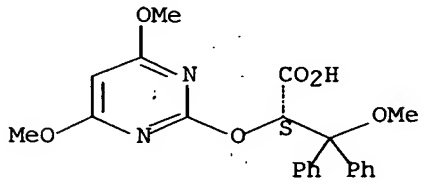
Absolute stereochemistry.



RE.CNT 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 55 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2002:816306 CAPLUS Full-text
DN 138:331443
TI Treatment with darusentan over 21 days improved cGMP generation in patients with chronic heart failure
AU Philipp, Sebastian; Monti, Jan; Pagel, Ines; Langenickel, Thomas; Notter, Thomas; Ruschitzka, Frank; Luescher, Thomas; Dietz, Rainer; Willenbrock, Roland
CS Franz-Volhard-Klinik, Helios Klinikum Berlin, Humboldt University, Berlin, 13125, Germany
SO Clinical Science (2002), 103(Suppl.), 249S-253S
CODEN: CSCIAE; ISSN: 0143-5221
PB Portland Press Ltd.
DT Journal
LA English
AB In heart failure, the cGMP to natriuretic peptide ratio is decreased and infusion of atrial natriuretic peptide (ANP) induces less cGMP generation. The ratio of the second messenger cGMP to plasma concns. of ANP or brain natriuretic peptide (BNP) correlates with the effectiveness of natriuretic peptides. It was investigated whether blockade of the ETA receptor might improve the cGMP:NP ratio in heart failure. Patients with chronic heart failure (mean age = 57 yr) received oral treatment with the ETA antagonist darusentan (either 30, 100, 300 mg/day or placebo) on top of standard therapy over a period of 21 days in a randomized, double-blind, placebo-controlled, multicenter study. Plasma concns. of ANP, BNP and cGMP were determined before randomization and after 21 days of treatment. In parallel with decreased pulmonary and systemic vascular resistance, 3 wk of oral treatment with the ETA receptor antagonist darusentan reduced BNP plasma levels and increased the cGMP:BNP ratio significantly. The improved cGMP:BNP ratio might reflect the ability of chronic ETA receptor blockade to facilitate the generation of the second messenger cGMP, which points towards a favorable modulation of the natriuretic peptide effector system, in addition to hemodynamic improvement in heart failure patients.
IT **171714-84-4**, Darusentan
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); BIOL (Biological study)
(darusentan treatment for 21 days improvement of cGMP generation in patients with chronic heart failure)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

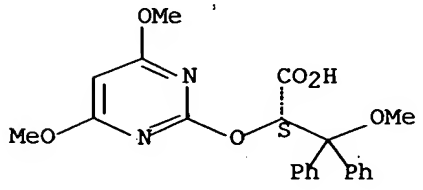
Absolute stereochemistry.



RE.CNT 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

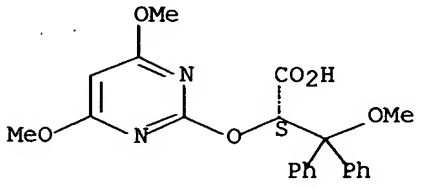
L11 ANSWER 56 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2002:816300 CAPLUS Full-text
DN 138:331441
TI The ETA receptor antagonist LU 135252 has no electrophysiological or anti-arrhythmic effects during myocardial ischaemia/reperfusion in dogs
AU Vago, Hajnalka; Soos, Pal; Zima, Endre; Geller, Laszlo; Kekesi, Violetta; Andrasi, Terezia; Szabo, Tamas; Juhasz-Nagy, Alexander; Merkely, Bela
CS Department of Cardiovascular Surgery, Semmelweis University Budapest, Budapest, H-1122, Hung.
SO Clinical Science (2002), 103(Suppl.), 223S-227S
CODEN: CSCIAE; ISSN: 0143-5221
PB Portland Press Ltd.
DT Journal
LA English
AB The anti-arrhythmic effects of ETA receptor antagonists during myocardial ischemia and reperfusion remain controversial. Moreover, the electrophysiol. mechanism has not yet been identified. The aim of this study was to investigate the potential anti-arrhythmic and electrophysiol. effects of the ETA receptor antagonist LU 135252 (LU) during myocardial ischemia and reperfusion in a canine model. A bolus of LU (1 mg/kg) or saline (control) was injected into the left anterior descending coronary artery before ligation of this vessel for 30 min, which was followed by a 90-min reperfusion period. LU bolus administration (0.5 mg/kg) was repeated every 30 min. There were no differences in mean arterial blood pressure or coronary blood flow between the two groups. The determined left ventricular ischemic mass was 25.5% and 27.8% of the total left ventricular mass in the control and LU groups resp. The total incidence of ventricular fibrillation during ischemia and reperfusion was 40% in the control and 50% in the LU group (not significantly different). The incidence of non-sustained and sustained ventricular tachycardias during ischemia, reperfusion and over the whole period (ischemia plus reperfusion) in the control group was 50%, 50% and 70% resp., and that in the LU group was 80%, 70% and 100% resp. (no significant differences between groups). The number of ventricular premature beats was not decreased by LU during either ischemia or reperfusion [median (25th-75th percentile): ischemia, 20 (13-37) and 56 (32-130) for LU and control groups resp.; reperfusion, 15 (2-21) and 39 (7-74) resp.; ischemia+reperfusion, 16 (4-35) and 43 (10-82) resp.; no significant differences between groups]. During ischemia, the monophasic action potential duration at 90% repolarization (MAPD90) decreased significantly, while during reperfusion a significant prolongation of MAPD90 was observed in the left anterior descending region that was similar in the two groups. In conclusion, LU did not affect repolarization changes and did not have anti-arrhythmic effects during either ischemia or reperfusion in this model.
IT **171714-84-4**, LU 135252
RL: PAC (Pharmacological activity); BIOL (Biological study)
(endothelin ETA receptor antagonist LU 135252 has no electrophysiol. or anti-arrhythmic effects during myocardial ischemia/reperfusion in dogs)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



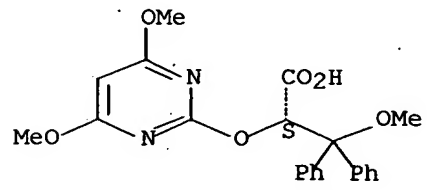
L11 ANSWER 57 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2002:816264 CAPLUS Full-text
DN 138:331435
TI ETA receptor blockade protects the small intestine against ischaemia/reperfusion injury in dogs via an enhancement of antioxidant defences
AU Andrasi, Terezia B.; Kekesi, Violetta; Blazovics, Anna; Dobi, Istvan; Szabo, Gabor; Juhasz-Nagy, Alexander
CS Department of Cardiovascular Surgery, Semmelweis University, Budapest, H-1122, Hung.
SO Clinical Science (2002), 103(Suppl.), 59S-63S
CODEN: CSCIAE; ISSN: 0143-5221
PB Portland Press Ltd.
DT Journal
LA English
AB The aim of the present study was to determine whether the ETA receptor antagonist LU 135252 can protect the mesentery against ischemia/reperfusion (I/R) damage. Direct occlusion of the superior mesenteric artery was performed for 30 min in two groups of dogs. Declamping was followed by 90 min of reperfusion. Mesenteric release of ET-1 was studied in series 1. In series 2, 5 min before cross-clamping, the treated group received an i.v. bolus of LU 135252 (5 mg/kg), whereas the control group was given vehicle. Mean arterial blood pressure and mesenteric blood flow were recorded. Mesenteric venous and systemic arterial serum lactate and glucose, plasma creatine kinase and free radical concns. were determined at 15 min intervals. Ischemia for 30 min induced a significant increase in mesenteric ET-1 release (1594 pg/min, compared with 343 pg/min at baseline), which had returned to baseline after 20 min of reperfusion. LU 135252 administration significantly decreased mesenteric blood flow during ischemia (204%) compared with controls (320%). In contrast, mesenteric blood flow was higher in the treated group (120% compared with 82%) after 90 min of reperfusion. Mesenteric lactate production was reduced by ETA antagonist administration under ischemia (0.77±0.02 mmol/L) compared with controls (1.36 mmol/L). Lower levels of venous creatine kinase were present in the treated group during ischemia as well as after reperfusion (120% compared with 150%). Administration of LU 135252 also improved the total scavenger capacity of the mesenteric bed during ischemia (15.9 + 106 compared with 6.4 + 106 relative light units) and early reperfusion (8.7 + 106 compared with 1.1 + 106 relative light units). Thus, ET-1 is involved in I/R-induced disturbances in the intestine. LU 135252 seems to counteract these changes, in part by increasing the antioxidant capacity of the mesentery.
IT **171714-84-4**, LU 135252
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(endothelin ETA receptor blockade protection of small intestine against mesenteric ischemia/reperfusion injury in dogs via enhancement of antioxidant defenses)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L11 ANSWER 58 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2002:816256 CAPLUS Full-text
DN 138:331434
TI The inhaled ETA receptor antagonist LU-135252 acts as a selective pulmonary vasodilator
AU Deja, Maria; Wolf, Steffen; Busch, Thilo; Petersen, Bodil; Jaghzies, Ursel; Boemke, Willehad; Kaisers, Udo
CS Klinik fuer Anaesthesiologie und Operative Intensivmedizin Charite, Campus Virchow-Klinikum, Medizinische Fakultaet der Humboldt-Universitaet, Berlin, D-13353, Germany
SO Clinical Science (2002), 103(Suppl.), 21S-24S
CODEN: CSCIAE; ISSN: 0143-5221
PB Portland Press Ltd.
DT Journal
LA English
AB To investigate the hypothesis that the inhaled ETA receptor antagonist LU-135252 acts as selective pulmonary vasodilator, we compared inhaled LU-135252 and inhaled nitric oxide (iNO) in an exptl. model of acute lung injury (ALI), in a prospective, randomized, controlled animal study. A total of 30 anesthetized, tracheotomized and mech. ventilated pigs underwent induction of ALI by repeated saline washout of surfactant. The animals were then randomly assigned to receive the nebulized ETA receptor antagonist LU-135252 (0.3 mg/kg, inhaled over 20 min; ETA-A group), inhaled NO (30 p.p.m. continuously; iNO group) or nebulized saline buffer (5 mL inhaled over 20 min; control group). Measurements of pulmonary gas exchange and hemodynamics were performed hourly over a 4 h period after induction of ALI. In the ETA-A group, the arterial oxygen tension (Pa02) increased from 58 to 377 mmHg at 4 h after intervention, while the intrapulmonary shunt (QS/QT) decreased from 53% to 18%. In the iNO group, Pa02 increased from 62 to 224 mmHg, and QS/QT decreased from 47% to 27%, at 4 h after induction of ALI. In the ETA-A and iNO groups, the increase in mean pulmonary artery pressure was significantly attenuated compared with controls (ETA-A group, 14±4%; iNO group, 6±4%; values at 4 h). In contrast, there were no significant differences in changes of mean arterial pressure and cardiac output between groups. Thus, in this exptl. model of ALI, both inhaled LU-135252 and iNO significantly improved gas exchange and prevented an increase in mean pulmonary artery pressure, without significant systemic effects, when compared with controls. Our results indicate the occurrence of selective pulmonary vasodilation in both treatment groups.
IT **171714-84-4**, LU-135252
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhaled endothelin ETA receptor antagonist LU-135252 acts as selective pulmonary vasodilator in pigs with acute lung injury)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

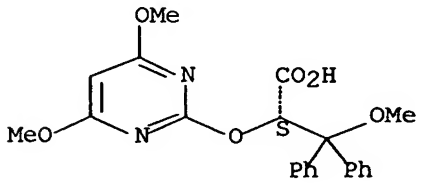
Absolute stereochemistry.



RE.CNT 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 59 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2002:816254 CAPLUS Full-text
DN 138:70999
TI Effects of obesity on endothelium-dependent reactivity during acute nitric oxide synthase inhibition: modulatory role of endothelin
AU Traupe, Tobias; D'Uscio, Livius V.; Muenter, Klaus; Morawietz, Henning; Vetter, Wilhelm; Barton, Matthias
CS Department of Internal Medicine and Medical Policlinic, University Hospital Zuerich, Zurich, CH-8091, Switz.
SO Clinical Science (2002), 103(Suppl.), 13S-15S
CODEN: CSCIAE; ISSN: 0143-5221
PB Portland Press Ltd.
DT Journal
LA English
AB This study investigated vascular reactivity in response to acetylcholine, in the presence of acute inhibition of nitric oxide synthase, in the carotid artery and aorta of obese C57B16/J mice fed on a high-fat diet for 30 wk, and of control mice. A subgroup of obese animals was also treated with the ETA receptor antagonist darusentan (50 mg·kg-1·day- 1). In vascular rings from control animals, acetylcholine caused endothelium-dependent contractions in the carotid artery, but not in the aorta. In vascular rings from obese mice, contractility to acetylcholine was also evident in the aorta, and that in the carotid artery was increased compared with control mice. ETA receptor blockade by darusentan treatment of the obese mice prevented enhanced vasoconstriction to acetylcholine, resulting in mild vasodilatation. Thus obesity increases endothelium-dependent vasoconstriction in the absence of endothelial nitric oxide. This effect can be completely prevented by chronic ETA receptor blockade, suggesting that endothelin modulates increased endothelium-dependent vasoconstriction in obesity.
IT **171714-84-4**, Darusentan
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(modulatory role of endothelin on effects of obesity on endothelium-dependent reactivity during acute nitric oxide synthase inhibition)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

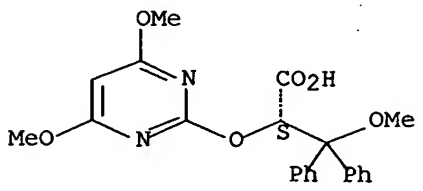
Absolute stereochemistry.



RE.CNT 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 60 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2002:809205 CAPLUS Full-text
DN 139:46710
TI Endothelin-A Receptor Blockade Prevents Left Ventricular Hypertrophy and Dysfunction in Salt-Sensitive Experimental Hypertension
AU Rothermund, Lars; Vetter, Roland; Dieterich, Maike; Kossmehl, Peter; Goegebakan, Oezlem; Yagil, Chana; Yagil, Yoram; Kreutz, Reinhold
CS B Institut fuer Klinische Pharmakologie, Freie Universitaet Berlin, Berlin, 12200, Germany
SO Circulation (2002), 106(18), 2305-2308
CODEN: CIRCAZ; ISSN: 0009-7322
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB Background- Salt-sensitive hypertension represents a major cause of left ventricular (LV) dysfunction. We therefore explored the potential effects of the selective endothelin-A (ETA) receptor antagonist darusentan on the development of hypertension, LV hypertrophy (LVH), and dysfunction in a genetic rat model of salt-sensitive hypertension. Methods and Results- Animals from the salt-sensitive Sabra rat strain (SBH/y) and the salt-resistant strain (SBN/y) were treated with either normal diet (SBH/y and SBN/y) or with deoxycorticosterone acetate (DOCA) and salt (SBN/y-DOCA and SBH/y-DOCA). Addnl. groups were treated with 50 mg/kg/day of darusentan (SBH/y-DOCA-DA and SBN/y-DOCA-DA). Systolic blood pressure and LV weight increased in response to DOCA only in the SBH/y strain (+75 mm Hg and +30%). LV end-diastolic pressure increased and -dP/dtmax decreased in SBH/y-DOCA compared with SBH/y. This was paralleled by a 5-fold upregulation of LV mRNA expression of atrial natriuretic factor (ANF) and a significant reduction of sarcoplasmic reticulum (SR) Ca2+-reuptake and the SR Ca2+-ATPase to phospholamban protein ratio (-30%). Whereas treatment with darusentan in SBH/y-DOCA-DA reduced the SBP increase by 50%, LVH elevation of ANF mRNA and LV dysfunction were completely prevented; this was associated with a normalization of SR Ca2+-reuptake and SR Ca2+-Atpase to phospholamban ratio by darusentan. A moderate elevation of interstitial fibrosis in SBH/y-DOCA remained unaffected by darusentan treatment. Conclusion- In the Sabra model of salt-sensitive hypertension, ETA-receptor blockade demonstrated striking effects on the prevention of LVH and LV dysfunction beyond its considerable antihypertensive effect.
IT **171714-84-4**, Darusentan
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(endothelin-A receptor blockade prevents left ventricular hypertrophy and dysfunction in salt-sensitive exptl. hypertension in rats)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

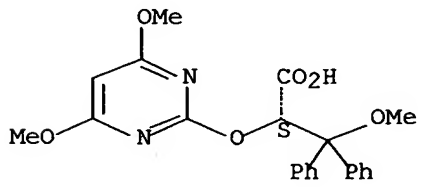
Absolute stereochemistry.



RE.CNT 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 61 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2002:739093 CAPLUS Full-text
DN 138:297310
TI Angiotensin-converting enzyme inhibition and endothelin antagonism for endothelial dysfunction in heart failure: mono- or combination therapy
AU Bauersachs, Johann; Fraccarollo, Daniela; Schaefer, Andreas; Ertl, Georg
CS Medizinische Klinik Julius-Maximilians-Universitat, Wurzburg, Germany
SO Journal of Cardiovascular Pharmacology (2002), 40(4), 594-600
CODEN: JCPCDT; ISSN: 0160-2446
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB The effect of angiotensin-converting enzyme (ACE) inhibition and endothelin A (ET) receptor antagonism alone and in combination on endothelial vasomotor dysfunction in chronic heart failure (CHF) was compared. Vasoreactivity and superoxide anion formation were determined in aortic rings from Wistar rats with exptl. CHF 12 wk after extensive myocardial infarction and compared with those in sham-operated animals. Rats were treated with placebo, with the ET receptor antagonist LU 135252 (30 mg/kg/day), with the ACE inhibitor trandolapril (0.3 mg/kg/day), or with a combination of LU 135252 and trandolapril. In the placebo group, the concentration-response curve of the endothelium-dependent, acetylcholine-induced relaxation was shifted to the right and the maximum relaxation was attenuated compared with the sham placebo group. Treatment with LU 135252 as well as with trandolapril improved acetylcholine-induced maximum relaxation. In addition to improving relaxation, combination therapy also improved the pathol. rightward shift. Increased superoxide production in CHF was reduced in all treatment groups. The increased relaxation elicited by exogenous superoxide dismutase in CHF was reduced to normal values by monotherapy and further attenuated by combination treatment. Although monotherapy with the ACE inhibitor trandolapril and the ET receptor antagonist LU 135252 improved endothelial dysfunction in exptl. CHF, combination therapy was more effective.
IT **171714-84-4**, LU 135252
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ACE inhibition (trandolapril) and endothelin antagonism (LU 135252) effect on endothelial dysfunction in heart failure)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

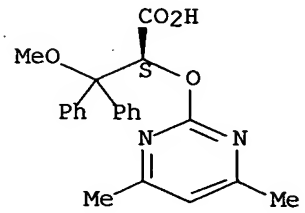
Absolute stereochemistry.



RE.CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 62 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2002:725341 CAPLUS Full-text
DN 138:348519
TI Administration of a selective endothelin-A receptor antagonist (BSF 208075) improves hepatic warm ischemia/reperfusion injury in pigs
AU Witzigmann, H.; Ludwig, S.; Escher, E.; Armann, B.; Gabel, G.; Teupser, D.; Tannapfel, A.; Pietsch, U. C.; Hauss, J.; Uhlmann, D.
CS Clinical Chemistry and Molecular Diagnostics, and Laboratory Medicine, Department of Surgery II and Anesthesiology and the Institutes of Pathology, University of Leipzig, Leipzig, Germany
SO Transplantation Proceedings (2002), 34(6), 2387-2388
CODEN: TRPPA8; ISSN: 0041-1345
PB Elsevier Science Inc.
DT Journal
LA English
AB In this study, we evaluate whether the selective ET-A receptor antagonist (ET-A-RA) BSF 208075 would improve hepatic warm ischemia/reperfusion injury in pigs. Total vascular exclusion was performed for 2 h under general anesthesia (thiopental, isoflurane, fentanyl) in 14 female German Landrace pigs (20 to 25 kg). Group 1-(n = 7) received 10 mg/kg b.w. i.v. of the specific ET-A-RA BSF 208075 and group 2-(n = 7) received an equivalent volume of normal saline solution We found a profound reduction of blood flow and partial oxygen tension PtiO2 through the liver in the postischemic period and suggest that ET is largely responsible for the disturbances in the microcirculation. The therapy group shows an improvement of erythrocyte flux and PtiO2 after reperfusion suggesting a maintained nutrient and oxygen supply to the postischemic liver. Therapy with the selective ET-A-RA significantly reduced hepatic histol. injury after 2 h of vascular exclusion. The blocking of ET-A receptors during ischemia/reperfusion hence offers a successful means of hepatoprotection by the maintenance of microvascular integrity in the postischemic liver.
IT **177036-94-1**, BSF 208075
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(administration of a selective endothelin-A receptor antagonist (BSF 208075) improves hepatic warm ischemia/reperfusion injury in pigs)
RN 177036-94-1 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethyl-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

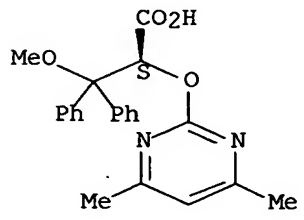
Absolute stereochemistry.



RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

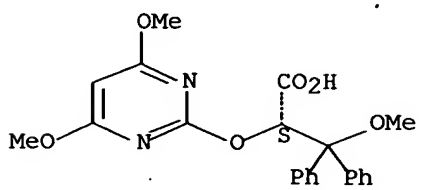
L11 ANSWER 63 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2002:725329 CAPLUS Full-text
DN 138:348518
TI Attenuation of endothelin expression and histologic changes by administration of a selective endothelin-A receptor antagonist in pig pancreas transplantation
AU Uhlmann, D.; Ludwig, S.; Escher, E.; Armann, B.; Gabel, G.; Teupser, D.; Tannapfel, A.; Pietsch, U. C.; Hauss, J.; Witzigmann, H.
CS Department of Surgery II, University of Leipzig, Leipzig, Germany
SO Transplantation Proceedings (2002), 34(6), 2362-2363
CODEN: TRPPA8; ISSN: 0041-1345
PB Elsevier Science Inc.
DT Journal
LA English
AB The aim of our study was to investigate the effectiveness of a selective endothelin-A receptor antagonist (ET-A-RA) in preventing ischemia/reperfusion injury in the context of pancreas transplantation with respect to histol. and electron microscopic injury and immunohistochem. expression of ET-1 and ET-A receptors. We used a pig model, which closely resembles human clin. pancreas transplantation. Group 1-(n = 7) received 10 mg/kg body weight IV of the specific ET-A-RA BSF 208075, and group 2-(n = 7) received an equivalent volume of normal saline solution In the central venous blood of the recipients plasma ET-1 levels of 0.82+0.2 pg/mL were measured in both groups before surgery. Before reperfusion, the levels rose significantly to 1.85 ± 0.63 pg/mL in the control and 1.62 ± 0.72 pg/mL in the therapy group. A further significant increase in the control group to a maximum of 3.48 ± 1.09 pg/mL was measured 2 h after reperfusion ($P < .05$). In the therapy group, levels of 24.6 ± 3.3 pg/mL were measured even 30 min after reperfusion due to the receptor blockade ($P < .05$ vs. control). Maximum levels of 33.1 ± 7.4 pg/mL were detected 1 h after reperfusion. Thereafter, similar to the control group, levels dropped to 2.4 ± 1.1 pg/mL at 5 days after transplantation. Histomorphol. anal. of pancreatic grafts 1 h after reperfusion and at postoperative days 2 and 5 revealed significantly less evidence of injury (ie, edema, hemorrhage, necrosis, leukocyte infiltration) in the therapy group in comparison to the control group ($P < .05$).
IT **177036-94-1**, BSF 208075
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(attenuation of endothelin expression and histol. changes reflecting ischemia/reperfusion injury by administration of a selective endothelin-A receptor antagonist in pig pancreas transplantation)
RN 177036-94-1 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethyl-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L11 ANSWER 64 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2002:706704 CAPLUS Full-text
DN 138:348471
TI Long-Term Survival and Hemodynamics After Endothelin-A Receptor Antagonism and Angiotensin-Converting Enzyme Inhibition in Rats With Chronic Heart Failure: Monotherapy versus Combination Therapy
AU Mulder, Paul; Boujedaini, Houssaine; Richard, Vincent; Henry, Jean-Paul; Renet, Sylvanie; Muenter, Klaus; Thuillez, Christian
CS Rouen University Medical School, Rouen, Fr.
SO Circulation (2002), 106(9), 1159-1164
CODEN: CIRCAZ; ISSN: 0009-7322
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB In patients with congestive heart failure (CHF) receiving ACE inhibitors, acute administration of selective endothelin (ET) antagonists addnl. improves systemic and cardiac hemodynamics. We investigated, in a rat model of CHF, whether such acute synergistic effects are sustained and accompanied, in the long term, by an addnl. limitation of left ventricular remodeling or an increase in survival. Rats were subjected to coronary artery ligation and treated for 3 or 9 mo with vehicle or with the ACE inhibitor trandolapril (Tr) (0.3 mg/kg-1 day-1), the ETA antagonist LU 135252 (LU, 30 mg/kg-1 day-1), or their combination starting 7 days after ligation. After 3 mo, the combination decreased LV systolic- and end-diastolic pressures (-32% and -80%, resp.) more markedly than Tr(-21% and -61%, resp.) or LU alone (-14% and -48%, resp.). Echocardiog. studies revealed that all treatments limited LV dilatation and increased LV fractional shortening and cardiac index. All treatments equally reduced left ventricular collagen d., increased LV fractional shortening and cardiac index. All treatments equally reduced left ventricular collagen d. whereas only Tr or the combination reduced LV weight Finally, although LU did not modify long-term survival, Tr and the combination of Tr and LU induced a similar improvement of survival. In this rat model, long-term combined administration of an ETA antagonist and an ACE inhibitor induces addnl. effects in terms of systemic and cardiac hemodynamics; however, this is not associated with an addnl. increase in long-term survival.
IT **171714-84-4**, LU 135252
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(long-term survival and hemodynamics after endothelin-A receptor antagonism and angiotensin-converting enzyme inhibition in rats with chronic heart failure)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

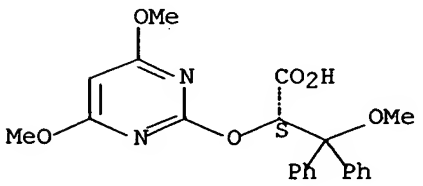
Absolute stereochemistry.



RE.CNT 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 65 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2002:612980 CAPLUS Full-text
DN 138:198354
TI Pharmacological prevention and regression of arterial remodeling in a rat model of isolated systolic hypertension
AU Dao, Huy Hao; Essalihi, Rachida; Graillon, Jean-Francois; Lariviere, Richard; De Champlain, Jacques; Moreau, Pierre
CS Faculty of Pharmacy, Universite de Montreal, Montreal, QC, H3C 3J7, Can.
SO Journal of Hypertension (2002), 20(8), 1597-1606
CODEN: JOHYD3; ISSN: 0263-6352
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB The efficacy of an endothelin-receptor antagonist (darusentan), an angiotensin-receptor blocker (irbesartan) and a thiazide diuretic (hydrochlorothiazide, HCTZ) in preventing and regressing pulse pressure (PP) elevation and remodeling of large and small arteries was studied in a rat model of isolated systolic hypertension (ISH) obtained by the chronic administration of warfarin and vitamin K1. Warfarin and vitamin K1 treatment for 4 or 8 wk led to an elevation of PP, associated with increases in aortic calcium deposition and the ratio of collagen to elastin (C/E). Despite these changes in the composition of the aortic wall, the global structure of the aorta was unchanged. In contrast, an outward hypertrophic remodeling was observed in the middle cerebral artery. An early treatment with darusentan, irbesartan, or HCTZ prevented the PP elevation, changes of aortic media composition and development of vascular remodeling. However, after 4 wk of ISH, only darusentan and irbesartan reduced PP when administered from week 4 to 8. Darusentan was the most effective in regressing existing aortic calcification, while only irbesartan reversed small-artery hypertrophic remodeling. During the development of ISH, drug treatment appears more beneficial when started early. The three agents prevented the PP elevation, aortic calcification and C/E increase in the aorta, and hypertrophy in small arteries. In contrast, once the disease is established, endothelin appears crucial in the maintenance of aortic calcification, while angiotensin II sustains small-artery hypertrophy.
IT **171714-84-4**, Darusentan
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(arterial remodeling in isolated systolic hypertension prevention and regression by)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 66 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2002:591553 CAPLUS Full-text
DN 137:154940
TI Preparation of thieno[2,3-d]pyrimidines as inhibitors of cGMP- and cAMP-phosphodiesterase (PDE V)
IN Eggenweiler, Hans-Michael; Eiermann, Volker; Schelling, Pierre
PA Merck Patent G.m.b.H., Germany
SO Ger. Offen., 40 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 10104802	A1	20020808	DE 2001-10104802	20010202
	CA 2437085	AA	20020815	CA 2002-2437085	20020114
	WO 2002062343	A2	20020815	WO 2002-EP256	20020114
	WO 2002062343	A3	20021121		
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PRAI	DE 2001-10104800	A	20010202		
	DE 2001-10104801	A	20010202		
	DE 2001-10104802	A	20010202		
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OS MARPAT 137:154940
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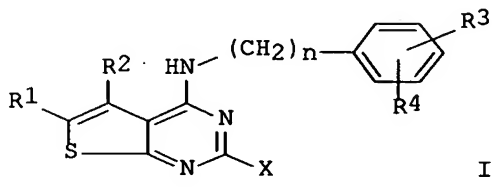


I

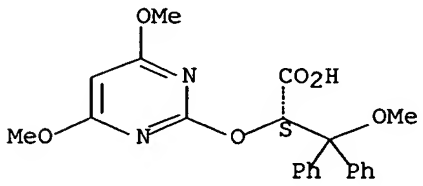
AB Pharmaceutical formylation containing title compds.. [I; R1, R2 = H, A, halo; or R1R2 = C3-5 alkylene; R3,R4 = H, A, OA, OH, halo; or R3R4 = C3-5 alkylene , OCH2CH2, OCH2O, OCH2CH2O; X = (CO2H-, CO2A-, CONH2-, CONHA-, CONA2-, cyano-substituted) (interrupted) alkylene, cycloalkylalkylene, C6H4(CH2)m; A = C1-6 alkyl; m = 1, 2; n = 0-3] and/or salts, and/or solvates thereof, and ≥1 endothelin receptor antagonist, is claimed. Thus, 2.2 g Me 3-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8- tetrahydro-[1]benzothieno[2,3-d]pyrimidin-2-yl]propionate (preparation given) was saponified with 32% NaOH to 2.0 g the corresponding propionic acid which was crystallized with HOCH2CH2NH2 to give 1.35 g 3-[4-(3-chloro-4- methoxybenzylamino)-5,6,7,8-tetrahydro-[1]benzothieno[2,3-d]pyrimidin-2- yl]propionic acid ethanolamine salt. I were said to show affinity for cGMP- and cAMP-phosphodiesterase (PDE V) (no data).

IT **171714-84-4 177036-94-1**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(endothelin receptor antagonist; for pharmaceutical formylation containing thienopyrimidines as inhibitors of cGMP- and cAMP-phosphodiesterase (PDE V))

RN 171714-84-4 CAPLUS

CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

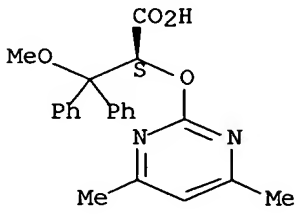
Absolute stereochemistry.



RN 177036-94-1 CAPLUS

CN Benzenepropanoic acid, α-[(4,6-dimethyl-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

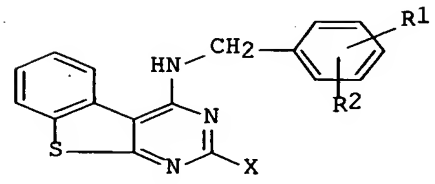
Absolute stereochemistry.



L11 ANSWER 67 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2002:591552 CAPLUS Full-text
DN 137:154939
TI Preparation of 4-benzylamino[1]benzothieno[2,3-d]pyrimidines as inhibitors of cGMP- and cAMP-phosphodiesterase (PDE V)
IN Eggenweiler, Hans-Michael; Eiermann, Volker; Schelling, Pierre
PA Merck Patent G.m.b.H., Germany
SO Ger. Offen., 38 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 10104801	A1	20020808	DE 2001-10104801	20010202
	CA 2437085	AA	20020815	CA 2002-2437085	20020114
	WO 2002062343	A2	20020815	WO 2002-EP256	20020114
	WO 2002062343	A3	20021121		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	EP 1357915	A2	20031105	EP 2002-702259	20020114
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	BR 2002006853	A	20040113	BR 2002-6853	20020114
	JP 2004525890	T2	20040826	JP 2002-562350	20020114
	US 2004063731	A1	20040401	US 2003-470763	20030731
PRAI	DE 2001-10104800	A	20010202		
	DE 2001-10104801	A	20010202		
	DE 2001-10104802	A	20010202		
	WO 2002-EP256	W	20020114		

OS MARPAT 137:154939
GI



I

AB Pharmaceutical formylation containing title compds. [I; R1, R2 = H, A, OA, OH, halo; or R1R2 = C3-5 alkylene, OCH2CH2, CH2OCH2, OCH2O, OCH2CH2O; X = (CO2H-, CO2A-, CONH2-, CONHA-, CONA2-, cyano-substituted) (interrupted) alkylene, cycloalkyl, cycloalkylalkylene, Ph, PhMe; A = C1-6 alkyl] and/or salts, and/or solvates thereof, and ≥1 endothelin receptor antagonist, is claimed. Thus, Me

4-(4-chlorobenzothieno[2,3-d]pyrimidin-2- yl)phenylcarboxylic acid ester was heated at 110° with 3-chloro-4-methoxybenzylamine in N-methylpyrrolidone for 4 h to give ca. 61% Me 4-[4-(3-chloro-4-methoxybenzylamino)[1]benzothieno[2,3-d]pyrimidin- 2-yl]benzoate. I were said to show affinity for cGMP- and cAMP-phosphodiesterase (PDE V) (no data).

IT **171714-84-4 177036-94-1**

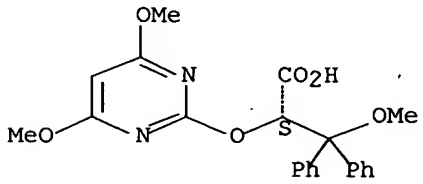
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(endothelin receptor antagonist; for pharmaceutical formylation containing benzothienopyrimidines as inhibitors of cGMP- and cAMP-phosphodiesterase (PDE V))

RN 171714-84-4 CAPLUS

CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

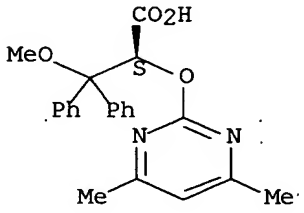
Absolute stereochemistry.



RN 177036-94-1 CAPLUS

CN Benzenepropanoic acid, α-[(4,6-dimethyl-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

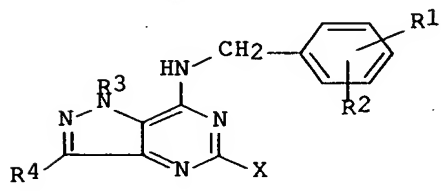
Absolute stereochemistry.



L11 ANSWER 68 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2002:591551 CAPLUS Full-text
DN 137:154938
TI Preparation of pyrazolo[4,3-d]pyrimidines as inhibitors of cGMP- and cAMP-phosphodiesterase (PDE V)
IN Eggenweiler, Hans-Michael; Eiermann, Volker; Schelling, Pierre
PA Merck Patent G.m.b.H., Germany
SO Ger. Offen., 38 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 10104800	A1	20020808	DE 2001-10104800	20010202
	CA 2437085	AA	20020815	CA 2002-2437085	20020114
	WO 2002062343	A2	20020815	WO 2002-EP256	20020114
	WO 2002062343	A3	20021121		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	EP 1357915	A2	20031105	EP 2002-702259	20020114
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	BR 2002006853	A	20040113	BR 2002-6853	20020114
	JP 2004525890	T2	20040826	JP 2002-562350	20020114
	US 2004063731	A1	20040401	US 2003-470763	20030731
	ZA 2003006819	A	20041201	ZA 2003-6819	20030901
PRAI	DE 2001-10104800	A	20010202		
	DE 2001-10104801	A	20010202		
	DE 2001-10104802	A	20010202		
	WO 2002-EP256	W	20020114		

OS MARPAT 137:154938
GI



I

AB Pharmaceutical formylation containing title compds. [I; R1, R2 = H, A, OA, OH, halo; or R1R2 = C3-5 alkylene, OCH2CH2, CH2OCH2, OCH2O, OCH2CH2O; R3, R4 = H, A; X = (CO2H-, CO2A-, CONH2-, CONHA-, CONA2-, cyano-substituted) (interrupted) alkylene, cycloalkyl, cycloalkylalkylene, Ph, PhMe; A = C1-6 alkyl] and/or

salts, and/or solvates thereof, and ≥1 endothelin receptor antagonist, is claimed. Thus, Me 4-[7-chloro-1-methyl-3-propyl- 1H-pyrazolo[4,3-d]pyrimidin-5-yl]phenylcarboxylic acid ester was heated at 110° with 3-chloro-4-methoxybenzylamine in N-methylpyrrolidone for 4 h to give ca. 54% Me 4-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3- propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl]benzoate. I were said to show affinity for cGMP- and cAMP-phosphodiesterase (PDE V) (no data).

IT **171714-84-4 177036-94-1**

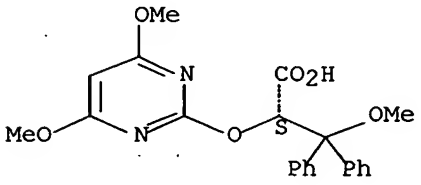
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(endothelin receptor antagonist; for pharmaceutical formylation containing pyrazolopyrimidines as inhibitors of cGMP- and cAMP-phosphodiesterase (PDE V))

RN 171714-84-4 CAPLUS

CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

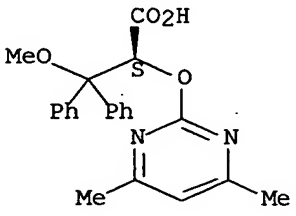
Absolute stereochemistry.



RN 177036-94-1 CAPLUS

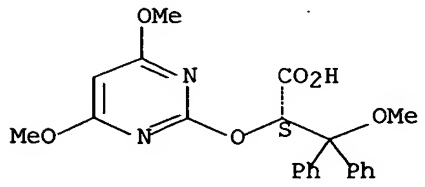
CN Benzenepropanoic acid, α-[(4,6-dimethyl-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L11 ANSWER 69 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2002:580740 CAPLUS Full-text
DN 137:149997
TI Darusentan: An effective endothelinA receptor antagonist for treatment of hypertension
AU Nakov, Roumen; Pfarr, Egon; Eberle, Siegfried
CS HEAT Investigators, Abbott GmbH and Co. KG, Ludwigshafen, D-67008, Germany
SO American Journal of Hypertension (2002), 15(7, Pt. 1), 583-589
CODEN: AJHYE6; ISSN: 0895-7061
PB Elsevier Science Inc.
DT Journal
LA English
AB The antihypertensive efficacy and safety of darusentan, a new selective endothelinA antagonist was investigated. In a multicenter randomized, double-blind, parallel-group, dose-response study, a 2-wk placebo run-in period was followed by a 6-wk treatment period and then a 2-wk placebo withdrawal period. At baseline before darusentan therapy, the average blood pressure (BP) of the patient population studied was diastolic 103.49 (SD 3.55) and systolic 168.27 (SD 16.63) mm Hg. In total, 392 patients were randomized (darusentan 10 mg: 94 patients, 30 mg: 103 patients, 100 mg: 96 patients, placebo: 99 patients). Darusentan significantly reduced diastolic (mean difference to placebo: 10 mg: -3.7 mm Hg, 95% confidence interval (CI): -6.6, -0.9, P = .009; 30 mg: -4.9 mm Hg, 95% CI: -7.7, -2.2, P = .0005; 100 mg: -8.3 mm Hg, 95% CI: -11.1, -5.5, P = .0001) and systolic BP (mean difference to placebo: 10 mg: -6.0 mm Hg, 95% CI: -11.0, -0.9, P = .02; 30 mg: -7.3 mm Hg, 95% CI: -12.3, -2.4, P = .004; 100 mg: -11.3 mm Hg, 95% CI: -16.3, -6.2, P = .0001). Pulse rate remained unchanged in all groups. There was a trend toward more adverse events in the active treatment groups (placebo: 30.3%, 10 mg: 44.7%, 30 mg: 40.8%, 100 mg: 49.0%). Headache was the most commonly reported adverse event, with no relevant difference among treatments. Flushing and peripheral edema were seen in a dose-dependent fashion in the active treatment groups only. These data, the first, suggest the therapeutic benefit of selective endothelinA receptor antagonism in human hypertension.
IT **171714-84-4**, Darusentan
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(darusentan: effective endothelin A receptor antagonist for treatment of patients with hypertension)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 70 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2002:555958 CAPLUS Full-text
DN 137:103936
TI Use of endothelin inhibitors for treatment or prevention of fibrotic disorders
IN Schuppan, Detlef; Raschack, Manfred
PA Germany
SO U.S. Pat. Appl. Publ., 10 pp., Division of U.S. Ser. No. 383,372.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2002098186	A1	20020725	US 2002-43317	20020114
PRAI	US 1999-383372	A3	19990826		

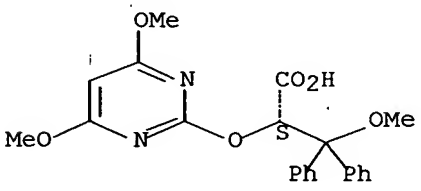
AB The invention discloses the use of endothelin inhibitors for treatment or prevention of fibrotic disorders.

IT **171714-84-4**, LU135252
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(endothelin inhibitors for treatment of fibrotic disorders)

RN 171714-84-4 CAPLUS

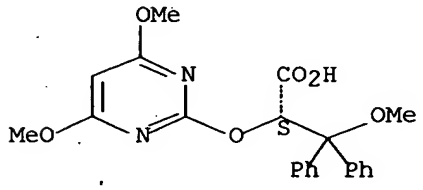
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L11 ANSWER 71 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2002:512957 CAPLUS Full-text
DN 138:83121
TI Endothelin A receptor antagonist LU 135252 inhibits hypercholesterolemia-induced, but not deendothelialization-induced, atherosclerosis in rabbit arteries
AU Tepe, Gunnar; Brehme, Ute; Seeger, Harald; Raschack, Manfred; Claussen, Claus D.; Duda, Stephan H.
CS Department of Diagnostic Radiology, University of Tuebingen, Tuebingen, Germany
SO Investigative Radiology (2002), 37(6), 349-355
CODEN: INVRAV; ISSN: 0020-9996
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB The purpose of the study was to test the capability of the endothelin A receptor antagonist LU 135252 to reduce neointimal formation in rabbits after balloon denudation with and without the presence of hypercholesterolemia. Twenty-eight male New Zealand White rabbits underwent balloon denudation of the infrarenal aorta. The animals were randomly assigned to 1 of the 4 groups. After balloon denudation, group 1 (n = 6) and 2 (n = 7) received a standard diet, and group 3 (n = 8) and 4 (n = 7) were fed a 0.5% cholesterol diet. All interventional procedures were performed while the rabbits were under general anesthesia. One week prior to intervention treatment with LU 135252 was started in group 2 and 4. After 6 wk the animals were killed for morphometric and histol. anal. Rabbits in all treatment groups developed neointimal hyperplasia. By addnl. systemic treatment with LU 135252, the mean neointima to media ratio was significantly reduced only in the hypercholesterolemic animals of group 4 (neointimal to media ratio area of group 3 vs group 4: 2.07 vs 1.41). ET receptor blockade in group 2 and 4 did not have an effect on plasma levels of cholesterol, very low-d. lipoprotein-, high-d. lipoprotein-, and low-d. lipoprotein-cholesterol. LU 135252 was efficient in reducing lipid induced atherosclerotic changes but was ineffective in inhibiting restenosis induced by balloon denudation.
IT **171714-84-4**, LU 135252
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(LU 135252 inhibits hypercholesterolemia-induced atherosclerosis)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

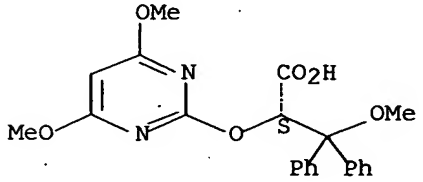
Absolute stereochemistry.



RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

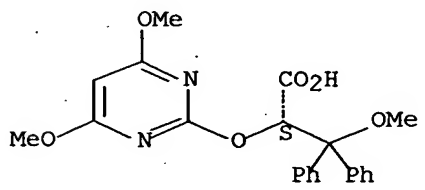
L11 ANSWER 72 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2002:440157 CAPLUS Full-text
DN 138:100603
TI Endothelin A-receptor antagonist administration immediately after experimental myocardial infarction with reperfusion does not affect scar healing in dogs
AU Basso, Cristina; Thiene, Gaetano; Della Barbera, Mila; Angelini, Annalisa; Kirchengast, Michael; Iliceto, Sabino
CS Institute of Pathological Anatomy, University of Padua Medical School, Padua, 35121, Italy
SO Cardiovascular Research (2002), 55(1), 113-121
CODEN: CVREAU; ISSN: 0008-6363
PB Elsevier Science B.V.
DT Journal
LA English
AB Objective: Endothelin (ET) receptor antagonists have been reported to reduce both infarct size and no-reflow phenomenon; however, in rat models their effect on the healing process after myocardial infarction (MI) is controversial. The study aimed to evaluate the effect of early administration of the ETA receptor antagonist darusentan on scar healing in an ischemia-reperfusion model in dogs. Methods: Thirty male mongrel dogs surviving 180 min left anterior descending coronary artery balloon occlusion were randomized to: darusentan i.v. bolus-5 mg/kg 5 min before reperfusion-(group I); darusentan i.v. bolus+chronic oral-10 mg/kg/day-(group II); saline (group III). Five age-matched dogs served as controls (group IV). At 6 wk weight, volume, mass/volume, wall thickness, thinning ratio and expansion index were assessed in the explanted hearts. Infarct size and scar area tissue composition were evaluated by computerized histomorphometry. Cellularity, vessels and TGFβ in the scar area were scored by immunohistochem. Results: 24 dogs (80%; 7 group I, 8 group II, 9 group III) developed an anterior MI, transmural in 15 and subendocardial in 9, mean size 11.5±4% of left ventricular area and 37±9% of left ventricular endocardial circumference. MIs were homogeneously distributed among the three groups regarding either infarct size or transmural extent. No differences were found in the three MI groups regarding thinning ratio, expansion index and scar area tissue characterization. Percent scar collagen content (37±17 vs. 53±20 vs. 46±14), myofibroblasts (1.2 vs. 1.3 vs. 1.4), macrophages (1.2±0.5 vs. 1.3±0.5 vs. 1.4±0.5), neovessels (2.8±0.4 vs. 2.6±0.5 vs. 2.9±0.3) and TGFβ score (2 vs. 2.25 vs. 2.11) were not significantly different. Conclusions: Early administration of the ETA receptor antagonist darusentan does not affect the scar healing process at 6 wk after exptl. MI with reperfusion in dogs.
IT **171714-84-4**, Darusentan
RL: PAC (Pharmacological activity); BIOL (Biological study)
(endothelin A-receptor antagonist administration immediately after exptl. myocardial infarction with reperfusion does not affect scar healing in dogs)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L11 ANSWER 73 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2002:299899 CAPLUS Full-text
DN 137:320091
TI Cardioprotection by long-term ETA receptor blockade and ACE inhibition in rats with congestive heart failure: mono- versus combination therapy
AU Fraccarollo, Daniela; Bauersachs, Johann; Kellner, Markus; Galuppo, Paolo; Ertl, Georg
CS Medizinische Klinik, Julius-Maximilians-Universitat Wurzburg, Wurzburg, D-97080, Germany
SO Cardiovascular Research (2002), 54(1), 85-94
CODEN: CVREAU; ISSN: 0008-6363
PB Elsevier Science B.V.
DT Journal
LA English
AB Objectives: We investigated the effects of long-term endothelin A (ETA) receptor blockade and ACE inhibition, either alone or in combination, on the hemodynamics, neurohormonal activation and cardiac remodeling in rats with congestive heart failure (CHF) after extensive myocardial infarction (MI). Methods: Rats were treated with placebo, the ETA antagonist LU135252 (30 mg/kg/d), the ACE inhibitor trandolapril (0.3 mg/kg/d), or a combination of both for 11 wk, starting 7 days after MI. Results: Despite comparable effects on left ventricular (LV) systolic pressure among all drug treatments, only combined ETA and ACE inhibition significantly reduced LV end-diastolic pressure ($P<0.01$), improved LV dP/dtmax ($P<0.01$) and normalized sympathetic activation ($P<0.05$) in rats with CHF. The combination therapy was more effective in reducing type I and III collagen mRNA levels, MMP-2 zymog. activity and collagen accumulation in the surviving LV myocardium. Moreover, the increases in cardiac β-myosin heavy chain and skeletal α-actin mRNAs, markers of hypertrophy or failure, were attenuated to a greater degree by the combination therapy than monotherapy, whereas right ventricular hypertrophy and ANF mRNA upregulation were significantly ($P<0.01$) prevented only by combined ETA and ACE inhibition. Conclusion: Long-term combined ETA receptor and ACE inhibition improved cardiac failure after extensive MI more effectively than monotherapy. We show additive effects on LV fibrosis and fetal gene expression. ETA receptor antagonists could be a therapeutical option in CHF in addition to an ACE inhibitor.
IT **171714-84-4**, LU135252
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cardioprotection by long-term ETA receptor blockade and ACE inhibition in rats with congestive heart failure: mono- vs. combination therapy)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

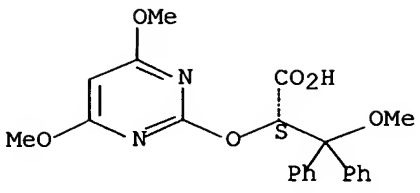
Absolute stereochemistry.



RE.CNT 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 74 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2002:205330 CAPLUS Full-text
DN 136:318740
TI Therapeutic potential for endothelin receptor antagonists in cardiovascular disorders
AU Spieker, Lukas E.; Noll, Georg; Luscher, Thomas F.
CS Cardiovascular Centre, Division of Cardiology, Institute of Physiology, University Hospital and Cardiovascular Research, Zurich, Switz.
SO American Journal of Cardiovascular Drugs (2001), 1(4), 293-303
CODEN: AJCDDJ; ISSN: 1175-3277
PB Adis International Ltd.
DT Journal; General Review
LA English
AB A review. The endothelins are synthesized in vascular endothelial and smooth muscle cells, as well as in neural, renal, pulmonal, and inflammatory cells. These peptides are converted by endothelin-converting enzymes (ECE-1 and -2) from "big endothelins" originating from large preproendothelin peptides cleaved by endopeptidases. Endothelin (ET)-1 has major influence on the function and structure of the vasculature as if favors vasoconstriction and cell proliferation through activation of specific ETA and ETB receptors on vascular smooth muscle cells. In contrast, ETB receptors on endothelial cells cause vasodilation via release of nitric oxide (NO) and prostacyclin. Addnl., ETB receptors in the lung are a major pathway for the clearance of ET-1 from plasma. Indeed, ET-1 contributes to the pathogenesis of important disorders as arterial hypertension, atherosclerosis, and heart failure. In patients with atherosclerotic vascular disease (as well as in many other disease states), ET-1 levels are elevated and correlate with the number of involved sites. In patients with acute myocardial infarction, they correlate with 1-yr prognosis. ET receptor antagonists have been widely studied in exptl. models of cardiovascular disease. In arterial hypertension, they prevent vascular and myocardial hypertrophy. Exptl., ET receptor blockade also prevents endothelial dysfunction and structural vascular changes in atherosclerosis due to hypercholesterolemia. In exptl. myocardial ischemia, treatment with an ET receptor antagonist reduced infarct size and prevented left ventricular remodeling after myocardial infarction. Most impressively, treatment with the selective ETA receptor antagonist BQ123 significantly improved survival in an exptl. model of heart failure. In many clin. conditions, such as congestive heart failure, both mixed ETA/B as well as selective ETA receptor antagonism ameliorates the clin. status of patients, i.e. symptoms and hemodynamics. A randomized clin. trial showed that a mixed ETA/B receptor antagonist effectively lowered arterial blood pressure in patients with arterial hypertension. In patients with primary pulmonary hypertension or pulmonary hypertension related to scleroderma, treatment with a mixed ETA/B receptor antagonist resulted in an improvement in exercise capacity. ET receptor blockers thus hold the potential to improve the outcome in patients with various cardiovascular disorders. Randomized clin. trials are under way to evaluate the effects of ET receptor antagonism on morbidity and mortality.
IT **171714-84-4**, Darusentan
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(therapeutic potential for endothelin receptor antagonists in cardiovascular disorders)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

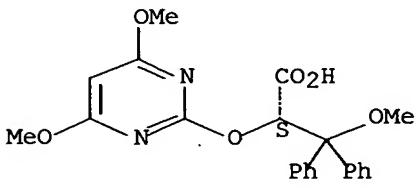
Absolute stereochemistry.



RE.CNT 201 THERE ARE 201 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 75 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2002:117867 CAPLUS Full-text
DN 137:241897
TI EARTH: EndothelinA Receptor Antagonist Trial in Heart Failure
AU Luescher, Thomas F.; Ruschitzka, Frank; Anand, Inder; Konstam, Marvin A.; McMurray, John; Notter, Thomas; Cohn, Jay N.
CS EARTH investigators, Cardiovascular Center, Cardiology, University Hospital, Zurich, Switz.
SO HeartDrug (2001), 1(6), 294-298
CODEN: HEARCO; ISSN: 1422-9528
PB S. Karger AG
DT Journal
LA English
AB Endothelin (ET) receptor blockade has been shown to have therapeutic potential in improving hemodynamics in exptl. and early clin. studies of heart failure. Whether and to what degree ETA blockade improves left ventricular function and clin. symptoms, however, still remains elusive. As such, the goal of the EARTH study is to evaluate the effects of different dosages of the orally available selective ETA receptor blocker LU 135252 (darusentan) on left ventricular dimensions, mass and function, neurohormone levels and symptoms in patients with advanced chronic heart failure. Patients with chronic heart failure functional class NYHA II-IV were included in the protocol and randomly assigned to receive darusentan (10, 25, 50, 100, 300 mg/day or matching placebo) in a double-blind design. Darusentan was titrated upwards over a 6-wk period, starting at 10 or 25 mg/day to a maximum of 300 mg/day with the total treatment period being 24 wk. The primary outcome was the effect of darusentan on left ventricular function as measured by end-systolic volume using magnetic resonance imaging compared to baseline. Secondary efficacy parameters were changes in left ventricular mass, left ventricular end-diastolic volume, ejection fraction, parameter of neurohumoral activation (plasma norepinephrine, aldosterone, ANP, BNP, ET-1 and big ET-1) and clin. symptoms assessed by a 6-min walk test, quality of life, and changes in NYHA class. The sample size of at least 600 patients (100 for each treatment group) was expected to provide 80% power to detect a difference in improvement of left ventricular end-systolic volume from a baseline of 18 mL with a 5% level of significance. A pos. result in the EARTH trial should stimulate the design of a large mortality/morbidity trial of ETA receptor blockers.
IT **171714-84-4**, LU 135252
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(endothelinA receptor antagonist trial in heart failure in humans)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

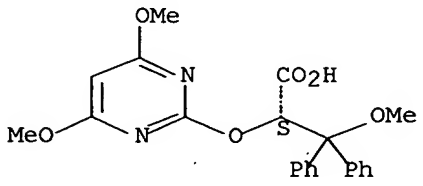
Absolute stereochemistry.



RE.CNT 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 76 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2002:53726 CAPLUS Full-text
DN 136:241008
TI Darusentan (Abbott Laboratories)
AU Lip, Gregory Y. H.
CS Haemostasis Thrombosis and Vascular Biology Unit City Hospital, University Department of Medicine, Birmingham, B18 7QH, UK
SO IDrugs (2001), 4(11), 1284-1292
CODEN: IDRUFN; ISSN: 1369-7056
PB Current Drugs Ltd.
DT Journal; General Review
LA English
AB A review. Abbott (formerly Knoll) is developing darusentan, an endothelin A antagonist, as a potential treatment for congestive heart failure (CHF). The compound entered phase II trials in Dec. 1998. In a model of monocrotaline-induced pulmonary hypertension, darusentan (50 mg/kg/day), significantly reduced right ventricular systolic pressure, and in a canine model of CHF chronic treatment for 2 wk significantly reduced left ventricular end diastolic pressure, mean pulmonary artery pressure, and right atrial pressure. Darusentan is a selective antagonist in vitro (ETA: Ki = 1.4 nM; ETB: Ki = 184 nM).
IT **171714-84-4**, Darusentan
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(darusentan for potential treatment of heart failure and hypertension in humans)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

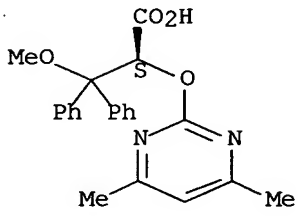
Absolute stereochemistry.



RE.CNT 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 77 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2002:8870 CAPLUS Full-text
DN 136:210330
TI Endothelin receptor blockade and in-stent restenosis
AU Kirchengast, Michael
CS Knoll AG, Ludwigshafen, D-67008, Germany
SO Journal of Cardiovascular Pharmacology (2001), 38(Suppl. 2), S31-S34
CODEN: JCPCDT; ISSN: 0160-2446
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB The aim of the present study was to test whether oral dosing of an endothelin (ET) receptor antagonist was able to reduce restenosis in the model of stent-induced restenosis. After pigs underwent coronary artery catheterization they were randomly allocated either to controls or to treatment with the ET receptor antagonist BSF 208075. Thirty-seven pigs underwent percutaneous transluminal coronary angioplasty plus stent implantation; seven animals died of ventricular fibrillation due to procedure-related myocardial ischemia. From the 30 surviving animals coronary arteries were sampled after 6 wk of oral treatment with 10 mg/kg/day BSF 208075 or vehicle and histol. evaluated. Stent implantation had no effect on total coronary artery diameter, and media thickness was virtually identical in the two groups. However, neointimal thickness in the group treated with the ET receptor antagonist was significantly reduced, resulting in a significantly larger total coronary artery lumen in the treated group. As in the setting of stent implantation neither "recoil" nor scar-related vascular remodelling can occur, this result allows the conclusion of a significant antiproliferative effect of ET receptor antagonism in pig coronary arteries.
IT **177036-94-1**, BSF 208075
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(endothelin receptor blockade and in-stent restenosis)
RN 177036-94-1 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethyl-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

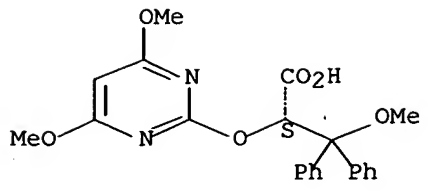
Absolute stereochemistry.



RE.CNT 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 78 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2002:4192 CAPLUS Full-text
DN 137:119319
TI Blood pressure-independent additive effects of pharmacologic blockade of the renin-angiotensin and endothelin systems on progression in a low-renin model of renal damage
AU Amann, Kerstin; Simonaviciene, Aurelia; Medwedewa, Tatiana; Koch, Andreas; Orth, Stephan; Gross, Marie-Luise; Haas, Christian; Kuhlmann, Alexander; Linz, Wolfgang; Scholkens, Bernward; Ritz, Eberhard
CS Departments of Pathology, University of Erlangen, Erlangen, D-91054, Germany
SO Journal of the American Society of Nephrology (2001), 12(12), 2572-2584
CODEN: JASNEU; ISSN: 1046-6673
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB Pharmacol. blockade of the renin and endothelin (ET) systems is an established strategy to interfere with progression of renal failure. In the Heyman nephritis model, additive benefits of decreases in BP with the combination of angiotensin-converting enzyme inhibitors (ACE-i) and ETA receptor antagonists (ET-RA) were demonstrated. To further investigate these findings and to exclude confounding effects of BP decreases, this issue was reassessed in a low-renin model of subtotal kidney resection. Subtotally nephrectomized (SNX) and sham-operated rats were left untreated or received an ACE-i, an angiotensin II subtype 1 receptor antagonist (AT1-RA), an ET-RA, or combinations thereof (ACE-i plus ET-RA or AT1-RA plus ET-RA). The parameters studied were the glomerulosclerosis index (GSI), tubulointerstitial index, vascular damage index, glomerular geometry, and albumin excretion. After 12 wk, BP values were comparable. Urinary albumin excretion rates were significantly higher for untreated SNX rats (24.3±31.3 mg/24 h), compared with untreated sham-operated rats (0.71±0.40 mg/24 h). Rates were significantly lower for all treated, compared with untreated, SNX groups. GSI values were significantly higher for untreated SNX rats than for untreated sham-operated rats. ACE-i caused significantly lower GSI in SNX rats (0.46±0.06), compared with AT1-RA (0.60±0.10) or ET-RA (0.65±0.10). GSI values were significantly decreased further with ACE-i plus ET-RA (0.29±0.09) or AT1-RA plus ET-RA (23±0.05) treatment. Changes in the tubulointerstitial index and vascular damage index proceeded in parallel. The results document BP-independent effects of the ACE-i and AT1-RA on the GSI and urinary albumin excretion and an effect of the ET-RA on the GSI. The contrasting results suggest different pathogenetic pathways for glomerulosclerosis and albuminuria. The combination of treatments provided superior effects on the GSI and tubulointerstitial index but not on urinary albumin excretion.
IT **171714-84-4**, LU 135252
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(blood pressure-independent additive effects of pharmacol. blockade of renin-angiotensin and endothelin systems on progression in low-renin model of renal damage in rats)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

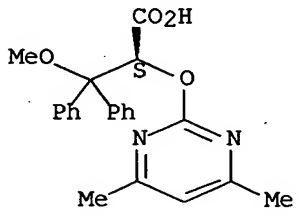
Absolute stereochemistry.



RE.CNT 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 79 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2001:922827 CAPLUS Full-text
DN 137:149935
TI Protective effect of a selective endothelin A receptor antagonist (BSF 208075) on graft pancreatitis in pig pancreas transplantation
AU Uhlmann, D.; Ludwig, S.; Escher, E.; Armann, B.; Gabel, G.; Teupser, D.; Tannapfel, A.; Hauss, J.; Witzigmann, H.
CS Department of Surgery II and Institute of Pathology,and of Laboratory Medicine, Clinical Chemistry, and Molecular Diagnostics, University of Leipzig, Leipzig, Germany
SO Transplantation Proceedings (2001), 33(7-8), 3732-3734
CODEN: TRPPA8; ISSN: 0041-1345
PB Elsevier Science Inc.
DT Journal
LA English
AB Twenty-eight mini-swine were submitted to a study to evaluate the effectiveness of a selective endothelin A (ETA) receptor antagonist in preventing ischemia-reperfusion injury in the context of pancreas transplantation with respect to microcirculation, morphol., and biochem. alterations. The recipients were divided into 2 groups, group I received i.v. 10 mg/kg BW of the ETA receptor antagonist, BSF 208075, and group II received an equivalent volume of normal saline solution Considerable ischemia-reperfusion injury was observed in the animal model of pancreas transplantation after 6 h of cold ischemia. Microcirculatory analyses showed a significant improvement by administration of the BSF 208075. Biochem., graft pancreatitis was less pronounced in the BSF 208075-treated group. The beneficial effect of the ETA receptor antagonist on pancreatitic microcirculation was characterized by improved blood flow and pancreatitic tissue values, indicating improved functional microvascular perfusion. These findings provide evidence that a selective ETA receptor antagonist, BSF 208075, has a protective effect on ischemia-reperfusion injury after pancreas transplantation.
IT **177036-94-1**, BSF 208075
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(protective effect of a selective endothelin A receptor antagonist on graft pancreatitis)
RN 177036-94-1 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethyl-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

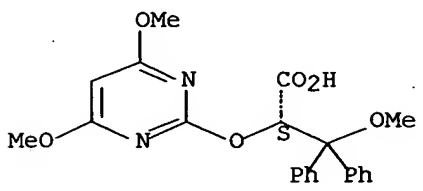
Absolute stereochemistry.



RE.CNT 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 80 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2001:908779 CAPLUS Full-text
DN 137:88115
TI Influence of aldosterone vs. endothelin receptor antagonism on renovascular function in licorice-induced hypertension
AU Quaschning, Thomas; Ruschitzka, Frank; Niggli, Bernhard; Lunt, Carolyn M. B.; Shaw, Sidney; Christ, Michael; Wehling, Martin; Luscher, Thomas F.
CS Institute of Physiology, Cardiovascular Research, University of Zurich, Switz.
SO Nephrology, Dialysis, Transplantation (2001), 16(11), 2146-2151
CODEN: NDTREA; ISSN: 0931-0509
PB Oxford University Press
DT Journal
LA English
AB 11β-Hydroxysteroid dehydrogenase type 2 (11β-HSD2) provides mineralocorticoid receptor specificity for aldosterone by metabolizing glucocorticoids to their receptor-inactive 11-dehydro derivs. Inhibition of 11β-HSD2 by licorice-derived glycyrrhizic acid (GA) therefore results in sodium retention and hypertension. This work investigated the effect of the aldosterone receptor antagonist spironolactone in comparison with the endothelin ETA receptor antagonist darusentan on renovascular endothelial function in liquorice-induced hypertension. GA, a recognized inhibitor of 11β-HSD2, was added to the drinking water (3 g/L) of Wistar-Kyoto rats for 21 days. From day 8 to 21, spironolactone (5.8 mg/kg/day), darusentan (45.2 mg/kg/day), or placebo was added to the chow. After the animals were killed, the function of isolated renal artery segments was assessed by isometric tension recording. Relaxation of preconstricted renal artery segments in response to acetylcholine (10-10-10-5M) was impaired by GA as compared with controls, whereas endothelium-independent relaxations were unaffected. Endothelin receptor antagonism improved renovascular endothelium-dependent relaxation, whereas this relaxation was completely normalized by aldosterone receptor antagonism. Thus, in GA-induced hypertension, both aldosterone receptor antagonism and endothelin receptor antagonism normalize blood pressure and improve renovascular function and may represent a new therapeutic approach in cardiovascular disease associated with impaired 11β-HSD2 activity.
IT **171714-84-4**, Darusentan
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aldosterone antagonism by spironolactone vs. endothelin receptor antagonism by darusentan effect on renal artery function in glycyrrhizic acid-induced hypertension)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 81 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2001:885732 CAPLUS Full-text
DN 136:11205
TI Combinations of an endothelin receptor antagonist and an antiepileptic compound having analgesic activity
IN Dooley, David James
PA Warner-Lambert Company, USA
SO PCT Int. Appl., 120 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001091736	A2	20011206	WO 2001-US14793	20010508
	WO 2001091736	A3	20021017		
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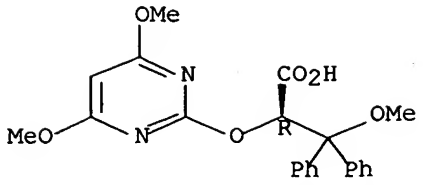
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	CA 2409927	AA	20011206	CA 2001-2409927	20010508
	EP 1289558	A2	20030312	EP 2001-939002	20010508
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	BR 2001011207	A	20030401	BR 2001-11207	20010508
	JP 2003535061	T2	20031125	JP 2001-587752	20010508
	US 2003232787	A1	20031218	US 2002-296792	20021126
PRAI	US 2000-208259P	P	20000531		
	WO 2001-US14793	W	20010508		

OS MARPAT 136:11205
AB The present invention is a novel combination effective for alleviating pain comprising an endothelin receptor antagonist or a salt and from 1 to 3 compds. independently selected from the group consisting of antiepileptics having analgesic activity, and pharmaceutical compns. comprising the compds. The administration of endothelin receptor antagonists in these novel combinations results in an improved reduction in the frequency and severity of pain. The incidence of unwanted side effects can be reduced by these novel combinations in comparison to using higher doses of a single agent treatment to achieve a similar therapeutic effect. Thus, tablets contained 4-(7-ethyl-1,3-benzodioxol-5-yl)-2-[2- (trifluoromethyl)phenyl]-2H-1,2-dihydro-1,2-benzothiazine-3-carboxylic acid 1,1-dioxide potassium salt 25, gabapentin 25, lactose 50, corn starch (for mix) 10, corn starch (paste) 10, and Mg stearate 5 mg. The combinations of the present invention are effective at reversing static allodynia,and are thus useful for the treatment of pain.
IT **221176-51-8**, Lu 127043
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Lu 127043; combinations of endothelin receptor antagonist and antiepileptic having analgesic activity)
RN 221176-51-8 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

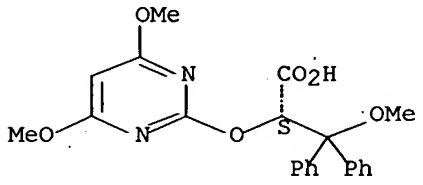


IT **171714-84-4 178306-66-6**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combinations of endothelin receptor antagonist and antiepileptic having analgesic activity)

RN 171714-84-4 CAPLUS

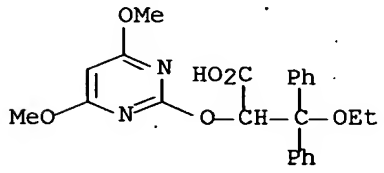
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



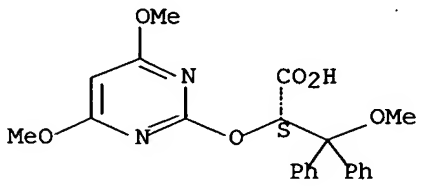
RN 178306-66-6 CAPLUS

CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-ethoxy-β-phenyl- (9CI) (CA INDEX NAME)



L11 ANSWER 82 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2001:834081 CAPLUS Full-text
DN 136:80150
TI Norepinephrine-induced aortic hyperplasia and extracellular matrix deposition are endothelin-dependent
AU Dao, Huy Hao; Lemay, Jacinthe; De Champlain, Jacques; DeBlois, Denis; Moreau, Pierre
CS Faculty of Pharmacy, Faculty of Medicine, University of Montreal, Montreal, QC, H3C 3J7, Can.
SO Journal of Hypertension (2001), 19(11), 1965-1973
CODEN: JOHYD3; ISSN: 0263-6352
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB Background: Sympathetic hyperactivity is observed in several disease states and may contribute to cardiovascular hypertrophic remodeling. Endothelin has been suggested to be a mediator of hypertrophy. Objective: To examine the involvement of endothelin in maintaining the growth response induced by exogenous norepinephrine. Design and methods: Rats were treated with norepinephrine (2.5 μg/kg/min, s.c.) for 2 and 4 wk, alone or in association with the selective endothelin-A (ETA) receptor antagonist, darusentan (LU 135252, 30 mg/kg/day, orally) for weeks 3 and 4. Results: Increases in medial cell number and accumulation of collagen and elastin characterized norepinephrine-induced aortic remodeling. These effects occurred without marked changes of mean arterial pressure, but may be related to enhanced pressure variability in addition to direct effects of norepinephrine. Inhibition of ETA receptors by darusentan reversed aortic alterations produced by infusion of norepinephrine. Evaluation of medial apoptosis did not reveal any significant change in any group at 4 wk. Conclusions: Antagonism of ETA receptors effectively and rapidly reversed norepinephrine-induced aortic structural and compositional changes, suggesting a central role of endothelin in mediating this response. Thus, ETA receptor antagonists may help to regress large artery remodeling in conditions of increased circulating catecholamine concns.
IT **171714-84-4**, LU 135252
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(norepinephrine-induced aortic hyperplasia and extracellular matrix deposition are endothelin-dependent)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

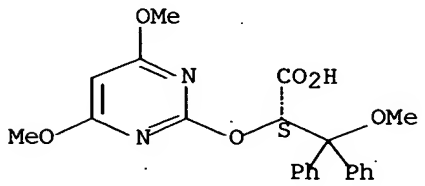
Absolute stereochemistry.



RE.CNT 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 83 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2001:821530 CAPLUS Full-text
DN 137:28015
TI Limitation of infarct size and attenuation of myeloperoxidase activity by an endothelin A receptor antagonist following ischaemia and reperfusion
AU Gonon, Adrian T.; Gourine, Andrey V.; Middelveld, Roelinde J. M.; Alving, Kjell; Pernow, John
CS Dept. of Cardiology, Karolinska Hospital, Stockholm, 17176, Swed.
SO Basic Research in Cardiology (2001), 96(5), 454-462
CODEN: BRCAB7; ISSN: 0300-8428
PB Steinkopff Verlag
DT Journal
LA English
AB It has previously been shown that endothelin (ET) receptor antagonists limit myocardial ischemia/reperfusion (I/R) injury. The mechanism behind this effect is still unclear. The aim of this study was to elucidate the possible relationship between cardioprotection by an ETA receptor antagonist and inhibition of neutrophil accumulation or activation in the myocardium determined as myeloperoxidase (MPO) activity during I/R. Anesthetized swine were subjected to 45 min ischemia by ligation of the left anterior descending coronary artery (LAD) followed by 4 h of reperfusion. Infiltration of MPO-containing cells, presumably neutrophils, into the ischemic area was confirmed with an immunohistochem. technique using antibodies against porcine MPO. Vehicle (n = 7) or the selective ETA receptor antagonist LU 135252 (LU; n = 7) were given into the LAD during the last 10 min of ischemia and the 1st 5 min of reperfusion. There were no significant differences in LAD flow, mean arterial pressure, heart rate, or rate pressure product between the groups during I/R. The area at risk was similar in the 2 groups. LU reduced the final infarct size to 40% of the area at risk compared to 80% in the vehicle group. Endothelin-like immunoreactivity increased 2-fold in the ischemic area in the vehicle group, but not in the group given LU. MPO activity was higher (2.5x) in the ischemic than in the non-ischemic myocardium of the vehicle group. The MPO activity in the ischemic myocardium was significantly lower in the group given LU (7.0 units g-1) than in the vehicle group (14.2 units g-1). There was a significant correlation between the infarct size and MPO activity. In conclusion, local administration of the selective ETA receptor antagonist LU during the last period of ischemia and early reperfusion reduces the extent of myocardial necrosis and MPO activity. This suggests that LU may exert its cardioprotective effect by inhibiting neutrophil-mediated injury.
IT **171714-84-4**, LU 135252
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(endothelin A receptor antagonist (LU 1352520) and cardioprotection in ischemia/reperfusion injury)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

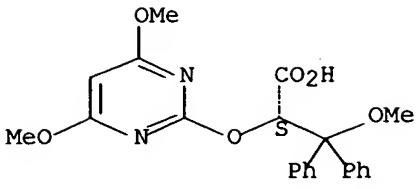
Absolute stereochemistry.



RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 84 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2001:560135 CAPLUS Full-text
DN 136:272903
TI Endothelin 1 type A receptor antagonism prevents vascular dysfunction and hypertension induced by 11β-hydroxysteroid dehydrogenase inhibition. Role of nitric oxide
AU Ruschitzka, Frank; Quaschning, Thomas; Noll, Georg; deGottardi, Andrea; Rossier, Michel F.; Enseleit, Frank; Hurlimann, David; Luscher, Thomas F.; Shaw, Sidney G.
CS Cardiovascular Research and Institute of Physiology, University Hospital Zurich, Zurich, Switz.
SO Circulation (2001), 103(25), 3129-3135
CODEN: CIRCAZ; ISSN: 0009-7322
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB Background: The enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD) prevents inappropriate activation of the nonselective mineralocorticoid receptors by glucocorticoids. Renal activity of 11β0-HSD is decreased in patients with apparent mineralocorticoid excess (SAME), licorice-induced hypertension, and essential hypertension. Although expressed in vascular cells, the role of 113-HSD in the regulation of vascular tone remains to be determined Methods and Results: Glycyrrhizic acid (GA; 50 mg/kg IP, twice daily for 7 days) caused a significant inhibition of 11β-HSD activity and induced hypertension in Wistar-Kyoto rats (157 vs. 127 mm Hg in controls; $P < 0.01$). After 11β-HSD inhibition, aortic endothelial nitric oxide (NO) synthase (eNOS) protein content, nitrate tissue levels, and acetylcholine-induced release of NO were blunted (all $P < 0.05$ vs. controls). In contrast, vascular prepro-endothelin (ET)-1 gene expression, ET-1 protein levels. and vascular reactivity to ET-1 were enhanced by GA treatment ($P < 0.05$ vs. controls). Chronic ETA receptor blockade with LU135252 (50 mg kg-1 d-1) normalized blood pressure, ET-1 tissue content, vascular reactivity to ET1., vascular eNOS protein content, and nitrate tissue levels and improved NO-mediated endothelial function in GA-treated rats ($P < 0.05$ to 0.01 vs. untreated and verapamil-treated controls). In human endothelial cells, GA increased production of ET-1 in the presence of corticosterone, which indicates that activation of the vascular ET-1 system by 11β-HSD inhibition can occur independently of changes in blood pressure but is dependent on the presence of glucocorticoids. Conclusions: Chronic ETA receptor blockade normalizes blood pressure, prevents up-regulation of vascular ET-1, and improves endothelial dysfunction in 11β-HSD inhibitor-induced hypertension and may emerge as a novel therapeutic approach in cardiovascular disease associated with reduced 11β-HSD activity.
IT **171714-84-4**, LU135252
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(endothelin 1 type A receptor antagonism prevents vascular dysfunction and hypertension induced by 11β-hydroxysteroid dehydrogenase inhibition. role of nitric oxide)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

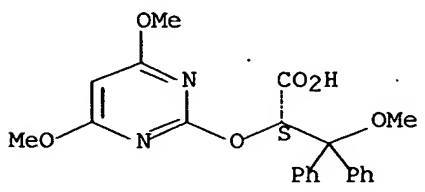
Absolute stereochemistry.



RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 85 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2001:488431 CAPLUS Full-text
DN 135:313380
TI Effect of ETA Receptor Antagonist on Pulmonary Hypertension and Vascular Reactivity in Rats With Congestive Heart Failure
AU Lucas, M.; Jasmin, J. F.; Dupuis, J.
CS Montreal Heart Institute, Research Center and Department of Medicine, Montreal, QC, H1T 1C8, Can.
SO Pulmonary Pharmacology & Therapeutics (2001), 14(4), 307-314
CODEN: PPTHFJ; ISSN: 1094-5539
PB Academic Press
DT Journal
LA English
AB Background: We evaluated the effects of chronic therapy with the selective ETA receptor antagonist LU 135252 (LU) on pulmonary vascular reactivity in congestive heart failure. Methods and Results: After myocardial infarction (MI) or sham operation, rats were gavaged with LU or saline for 4 wk. Studies were performed in isolated lungs and to differentiate acute from chronic effects, some expts. were performed with LU in the perfusate. The MI+saline group developed moderate pulmonary hypertension (PH) and right ventricular hypertrophy (RVH). This was improved by LU therapy despite no change in left ventricular function and a larger scar area. Vasodilation to sodium nitroprusside (SNP) was reduced after MI and modestly improved by LU therapy. Vasodilation to acetylcholine (Ach) was similar among the four groups, but accentuated after acute LU administration in the sham+saline and MI+saline groups. A23187 produced higher vasoconstriction (18±4%) in the MI+LU compared to the MI+saline (10±3%, $P<0.05$) and the two control groups (3±1% and 4±3%, with and without LU, $P<0.01$): this was reversed to vasodilation following the acute addition of LU. Conclusion: ETA receptor blockade after MI reduces PH and RVH. LU therapy mildly improves dilation to SNP and favorably modulates pulmonary endothelium-dependent responses. These results support future studies to better define the mechanisms of improvement in pulmonary vascular reactivity after ET receptor antagonist therapy. (c) 2001 Academic Press.
IT **171714-84-4**, LU 135252
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effect of ETA receptor antagonist on pulmonary hypertension and vascular reactivity in rats with congestive heart failure)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

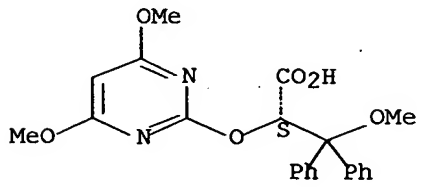
Absolute stereochemistry.



RE.CNT 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 86 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2001:309368 CAPLUS Full-text
DN 135:102273
TI Involvement of nitric oxide in cardioprotective effect of endothelin receptor antagonist during ischemia-reperfusion
AU Gourine, Andrey V.; Gonon, Adrian T.; Pernow, John
CS Department of Cardiology, Karolinska Hospital, Stockholm, S-171 76, Swed.
SO American Journal of Physiology (2001), 280(3, Pt. 2), H1105-H1112
CODEN: AJPHAP; ISSN: 0002-9513
PB American Physiological Society
DT Journal
LA English
AB The interaction between the cardioprotective effect of endothelin (ET) receptor blockade and nitric oxide (NO) during ischemia-reperfusion injury was investigated. Anesthetized pigs were subjected to 45 (protocol 1) or 30 min (protocol 2) coronary artery ligation and 4 h reperfusion. In protocol 1, five groups were given vehicle, the ETA receptor antagonist LU-135252 (LU), the NO synthase (NOS) inhibitor NG-nitro-L-arginine (L-NNA), L-NNA in combination with LU, or L-NNA in combination with the NO precursor L-arginine (L-Arg) and LU i.v. before ischemia. In protocol 2, two groups were given vehicle or L-NNA. In protocol 1, the infarct size (IS) was 79 ± 5% of the area at risk in the vehicle group and 93 ± 2% in the L-NNA group. LU reduced the IS to 43 ± 7% ($P < 0.001$). The cardioprotective effect of LU was abolished in the presence of L-NNA (IS 76 ± 6%), whereas addition of L-Arg restored its cardioprotective effect (IS 56 ± 2%; $P < 0.05$ vs. vehicle and L-NNA + LU groups). In protocol 2, the IS was 49 ± 6% in the vehicle group and 32 ± 4% in the L-NNA group (P = not significant). Myocardial ET-like immunoreactivity (ET-LI) increased in the vehicle group of protocol 1. ET-LI in the ischemic-reperfused myocardium was lower in the groups given LU ($P < 0.01$) and L-NNA + L-Arg + LU ($P < 0.05$) but not in the group given L-NNA + LU compared with the vehicle group. These results suggest that the cardioprotective effect of the ETA receptor antagonist is mediated via a mechanism related to NO.
IT **171714-84-4**, LU-135252
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cardioprotective effect of endothelin receptor antagonist during ischemia-reperfusion is mediated via mechanism related to nitric oxide)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

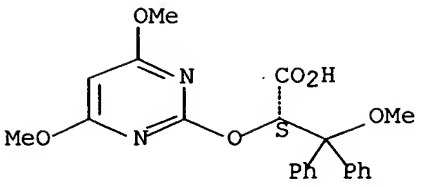
Absolute stereochemistry.



RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 87 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2001:240875 CAPLUS Full-text
DN 135:55811
TI Therapeutic administration of an endothelin-A receptor antagonist after acute ischemic renal failure dose-dependently improves recovery of renal function
AU Knoll, Thomas; Schult, Sabine; Birck, Rainer; Braun, Claude; Michel, Maurice S.; Bross, Stefan; Juenemann, Klaus-Peter; Kirchengast, Michael; Rohmeiss, Peter
CS Department of Urology, University Hospital Mannheim, Mannheim, D-68135, Germany
SO Journal of Cardiovascular Pharmacology (2001), 37(4), 483-488
CODEN: JCPCDT; ISSN: 0160-2446
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB Endothelin (ET) is known to reduce glomerular filtration rate and renal blood flow and is a possible mediator of acute renal failure (ARF). We recently demonstrated that the administration of a very high dose of the ETA-receptor antagonist LU 135252 (LU) accelerates recovery from postischemic acute renal failure by an improvement of renal perfusion in a rat model. The aim of this study was to investigate whether this effect of LU is dose dependent. ARF was induced in rats by clamping both renal arteries. Serum creatinine was measured and endogenous creatinine clearance and fractional sodium excretion were calculated up to 4 days after acute ischemia. Rats were treated either with the selective ETA-receptor antagonist LU or with vehicle only after reperfusion. LU in doses of 0.5, 1, or 5 mg/kg per day was infused via a femoral vein using an osmotic minipump. Serum creatinine was increased approx. eightfold after induction of ARF. Creatinine clearance decreased from 4.35 ± 0.26 mL/min before acute renal failure to 0.15 ± 0.02, 0.54 ± 0.1, and 1.49 ± 0.19 mL/min on days 1, 2, and 4 after ischemia ($p < 0.05$). Fractional sodium excretion increased from baseline 0.77 ± 0.05% to 7.5 ± 1.21% on day 1 and 8.53 ± 1.34% on day 2 ($p < 0.05$). Treatment with LU improved kidney function dose relatedly. There was no significant change in creatinine clearance, but compared with controls, with doses of 0.5 mg/kg per day and 1 mg/kg per day (0.28 ± 0.1, 0.88 ± 0.22, and 1.93 ± 0.24 mL/min on days 1, 2, and 4), we noted a significant increase under 5 mg/kg per day (day 1: 0.62 ± 0.17 mL/min; day 2: 1.38 ± 0.26 mL/min; and day 4: 2.45 ± 0.21 mL/min; $p < 0.05$). Fractional sodium excretion decreased dose-relatedly to a maximally 2.48 ± 0.58% on day 1 and 2.25 ± 0.71 % on day 2 after treatment with the highest dose when compared with untreated control rats ($p < 0.05$). Our data support the hypothesis that ET plays a major role in ARF. It can be concluded from these results that recovery from ischemic ARF is significantly and dose-dependently enhanced by treatment with a selective ETA-receptor antagonist.
IT **171714-84-4**, LU 135252
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(endothelin-A receptor antagonist LU 135252 improves recovery of renal function after acute ischemic renal failure)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

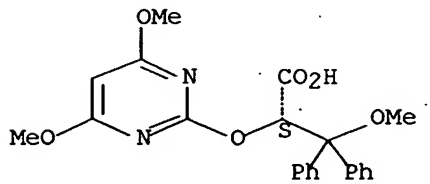
Absolute stereochemistry.



RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 88 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2001:224911 CAPLUS Full-text
DN 135:174986
TI Effects of endothelin A receptor blockade on endothelial function in patients with chronic heart failure
AU Berger, Rudolf; Stanek, Brigitte; Huilsmann, Martin; Frey, Bernhard; Heher, Sandra; Pacher, Richard; Neunteufl, Thomas
CS Dep. Cardiology, Univ. Vienna, Vienna, Austria
SO Circulation (2001), 103(7), 981-986
CODEN: CIRCAZ; ISSN: 0009-7322
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB Chronic heart failure (CHF) is associated with impaired endothelium-dependent vasodilation and increased basal vascular tone due, in part, to elevated endothelin-1 plasma levels. In the present study, we investigated whether a reduction of vascular tone using an endothelin A receptor blocker attenuates the impairment of endothelium-dependent, flow-mediated vasodilation (FMD). Twenty-one patients with CHF randomly received either the endothelin A receptor blocker LU 135252 (30 mg/d, n=7; 300 mg/d, n=7) or a placebo (n=7). Using high-resolution ultrasound, FMD and endothelium-independent, nitroglycerin-induced dilation of the brachial artery were assessed at baseline in the 21 patients with CHF and in 11 controls and after 3 wk treatment in the 21 patients with CHF. FMD at baseline was impaired in all 21 patients with CHF (3.2±2%) when compared with the 11 controls (9.7±4.9%; P=0.0005). In comparison with baseline, FMD significantly improved after 3 wk of treatment with LU 135252 in all 14 patients receiving it (from 3.0±2.0% to 4.9±2.9%; P=0.04), but FMD remained unchanged with placebo. Subgroup anal., according to different dosages, revealed a significant increase of FMD compared with baseline (from 2.4±1.5% to 5.5±2.4%; P=0.03) in the patients treated with the low-dose (30 mg/d), whereas a high dose of 300 mg/d failed to increase FMD significantly. Improvement in the high-dose group, however, may have been masked by reduced vasodilator capacity due to a significant increase in vessel size (from 4.8±0.4 to 5.1±0.7 mm; P=0.03). These results suggest that endothelin A receptor blockade improves FMD in CHF patients.
IT **171714-84-4**, LU 135252
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of LU 135252, a specific endothelin A receptor antagonist, on endothelial function in humans with chronic heart failure)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

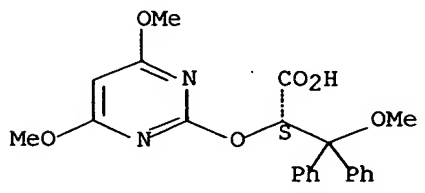
Absolute stereochemistry.



RE.CNT 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 89 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2001:223438 CAPLUS Full-text
DN 134:305144
TI Effects of endothelin receptor antagonists on the progression of diabetic nephropathy
AU Hocher, Berthold; Schwarz, Anja; Reinbacher, Daniel; Jacobi, Jaqueline; Lun, Andreas; Priem, Friedrich; Bauer, Christian; Neumayer, Hans-H.; Raschack, Manfred
CS Department of Nephrology, Humboldt University of Berlin, Ludwigshafen, Germany
SO Nephron (2001), 87(2), 161-169
CODEN: NPRNAY; ISSN: 0028-2766
PB S. Karger AG
DT Journal
LA English
AB Diabetic nephropathy is the leading cause of end-stage renal disease in European countries and is associated with an enhanced renal synthesis of endothelin (ET)-1. ETs are - beside its potent vasoconstrictor properties - very potent profibrotic acting paracrine hormones especially in the kidney. The authors analyzed in rats with streptozotocin-induced diabetes the effects of an ETA-type (ETA) receptor antagonist (LU 135252) in comparison to a combined ETA/ETB receptor antagonist (LU 224332) on the expression of interstitial and glomerular collagen type I, III and IV as well as on fibronectin and laminin by quant. immunohistochem. using a computer-aided image anal. system. Global glomerular matrix deposition was analyzed after PAS staining. In addition to the morphometric examination of the kidneys, the authors also investigated GFR, urinary albumin and total protein excretion. The diabetic rats were treated for 36 wk. Treatment with either LU 135252 or LU 224332 normalized the amount of PAS-pos. material within the glomeruli. The expression of glomerular fibronectin and type IV collagen was increased 36 wk after induction of diabetes. The overexpression of these two matrix proteins within the glomeruli of diabetic rats was completely abolished by both ET receptor antagonists, whereas protein excretion was only reduced by about 50% as compared to diabetic rats without treatment. The present study indicates that ETA receptor antagonists as well as combined ETA/ETB receptor antagonists reduce proteinuria and completely normalize the renal matrix protein expression in hyperglycemic rats with streptozotocin-induced diabetes. The antifibrotic effect seems to be mediated via the ETA receptor. ET receptor antagonists might be a new approach in the treatment of diabetic nephropathy.
IT **171714-84-4**, LU 135252
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)(endothelin receptor antagonists effects on progression of diabetic nephropathy)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

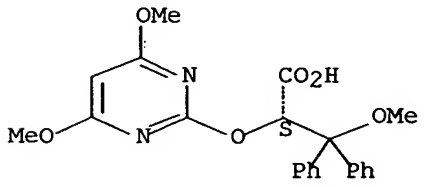
Absolute stereochemistry.



RE.CNT 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 90 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2001:112189 CAPLUS Full-text
DN 135:116893
TI Effectiveness of a nonselective ETA/B and a selective ETA antagonist in rats with monocrotaline-induced pulmonary hypertension
AU Jasmin, Jean-Francois; Lucas, Martin; Cernacek, Peter; Dupuis, Jocelyn
CS Department of Medicine, Montreal Heart Institute and the Royal Victoria Hospital, Montreal, QC, Can.
SO Circulation (2001), 103(2), 314-318
CODEN: CIRCAZ; ISSN: 0009-7322
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB Background-Both nonselective ETA/B receptor and selective ETA receptor antagonists can reduce pulmonary hypertension (PH) and right ventricular hypertrophy (RVH) in various animal models. Depending on their net effects after blockade of endothelial and smooth muscle ETB receptors, nonselective ETA/B antagonists could be more or less effective than selective ETA antagonists. Methods and Results-Two weeks after injection of saline or 60 mg/kg monocrotaline (MCT), rats received 50 mg/kg/d of a selective (LU 135252) or nonselective (BSF 420627) antagonist for 3 wk. This resulted in 4 groups: control, MCT, MCT+ETA, and MCT+ETA/B. Five-week survival was 35% in the MCT group; this was increased to 56% in the MCT+ETA group and to 67% in the MCT+ETA/B group. Drug administration was stopped 48 h before hemodynamic measurements to evaluate the chronic effects of therapy: PH in the MCT group (RV systolic pressure 87 mm Hg) was improved similarly in both MCT+ETA and MCT+ETA/B groups (72 and 70 mm Hg, resp.). Severe RVH in the MCT group (RV/left ventricle+septum weight ratio 73%) was not affected by the selective antagonist (70%) but was reduced to 54% in the MCT+ETA/B group. Pulmonary resistive properties, assessed from isolated lung pressure-flow relationships, were improved similarly in survivors from both treated groups. Conclusions-Both the nonselective ETA/B antagonist BSF 420627 and the selective ETA antagonist LU 35252 are effective in this model of PH. Similar direct comparative studies in other models of PH and with various dosage regimens are warranted to define the optimal pharmacol. approach of PH when ET receptor antagonists are used.
IT **171714-84-4**, LU 135252
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(endothelin nonselective ETA/B and selective ETA receptor antagonist efficacy in rats with monocrotaline-induced pulmonary hypertension)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 91 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2001:63980 CAPLUS Full-text
DN 134:131546
TI Preparation of pyrimidinyloxypropionates as endothelin receptor antagonists.
IN Amberg, Wilhelm; Kettschau, Georg
PA Basf Aktiengesellschaft, Germany
SO PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DT Patent
LA German
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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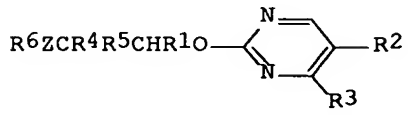
	CA 2379545	AA	20010125	CA 2000-2379545	20000705
	EP 1196394	A1	20020417	EP 2000-953009	20000705
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	BR 2000012592	A	20020528	BR 2000-12592	20000705
	CN 1367778	A	20020904	CN 2000-810533	20000705
	JP 2003505377	T2	20030212	JP 2001-511432	20000705
	TW 555749	B	20031001	TW 2000-89113992	20000713
	ZA 2002000333	A	20030217	ZA 2002-333	20020115
	NO 2002000254	A	20020220	NO 2002-254	20020117
	BG 106321	A	20020830	BG 2002-106321	20020118
	KR 2002019550	A	20020312	KR 2000-700815	20020119
PRAI	DE 1999-19933164	A	19990720		
	WO 2000-EP6293	W	20000705		

OS MARPAT 134:131546
GI



I

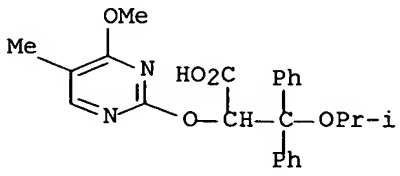
AB Title compds. [I; R = tetrazolyl, acyl; R2 = OH, amino, alkyl, alkenyl, alkynyl, hydroxyalkyl, alkylthio, etc.; R3 = OH, amino, halo, alkyl, alkenyl, alkynyl, alkenyloxy, haloalkyl, alkoxy, haloalkoxy, alkylthio, etc.; R2R3 = atoms to form a 5-6 membered ring; R4, R5 = (substituted) Ph, naphthyl, cycloalkyl; R6 = H, (substituted) alkyl, alkenyl, alkynyl, Ph, naphthyl, heteroaryl; Z = O, S], were prepared Thus, a suspension of NaH in DMF at 0° was treated with (S)-2-hydroxy-3-methoxy-3,3- diphenylpropionic acid in DMF and then with 2-methylsulfonyl-4-methoxy-5- methylpyrimidine (preparation given) in DMF followed by stirring overnight to give (S)-2-(4-methoxy-5-methylpyrimidin-2-yloxy)-3-methoxy-3,3- diphenylpropionic acid. The latter showed Ki = 0.6 nM for binding to ETA receptors.

IT **321655-48-5P 321655-51-0P 321655-52-1P**
321655-54-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);

BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of pyrimidinyloxypropionates as endothelin receptor antagonists)

RN 321655-48-5 CAPLUS

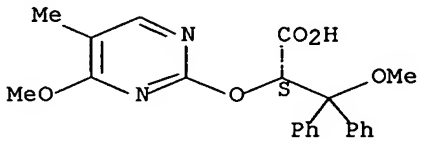
CN Benzenepropanoic acid, α-[(4-methoxy-5-methyl-2-pyrimidinyl)oxy]-β-(1-methylethoxy)-β-phenyl- (9CI) (CA INDEX NAME)



RN 321655-51-0 CAPLUS

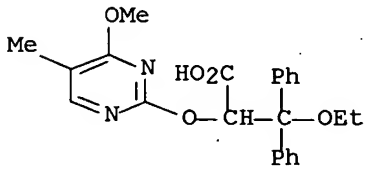
CN Benzenepropanoic acid, β-methoxy-α-[(4-methoxy-5-methyl-2-pyrimidinyl)oxy]-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



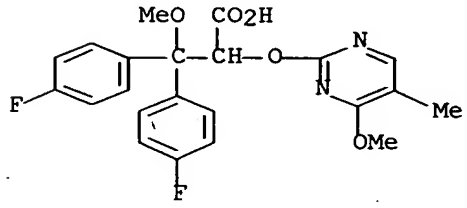
RN 321655-52-1 CAPLUS

CN Benzenepropanoic acid, β-ethoxy-α-[(4-methoxy-5-methyl-2-pyrimidinyl)oxy]-β-phenyl- (9CI) (CA INDEX NAME)



RN 321655-54-3 CAPLUS

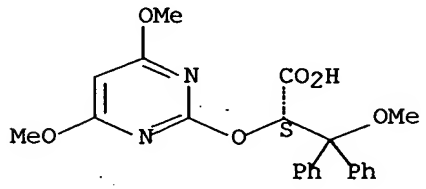
CN Benzenepropanoic acid, 4-fluoro-β-(4-fluorophenyl)-β-methoxy-α-[(4-methoxy-5-methyl-2-pyrimidinyl)oxy]- (9CI) (CA INDEX NAME)



RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 92 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2001:23076 CAPLUS Full-text
DN 135:70937
TI Ischemia-reperfusion injury at the microvascular level: Treatment by endothelin A-selective antagonist and evaluation by myocardial contrast echocardiography
AU Galiuto, Leonarda; DeMaria, Anthony N.; del Balzo, Ughetta; May-Newman, Karen; Flaim, Stephen F.; Wolf, Paul L.; Kirchengast, Michael; Iliceto, Sabino
CS Division of Cardiovascular Medicine, University of California at San Diego, San Diego, USA
SO Circulation (2000), 102(25), 3111-3116
CODEN: CIRCAZ; ISSN: 0009-7322
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB The purpose of this study was to verify whether endothelin A-antagonist administration at the time of coronary reperfusion preserves postischemic microvasculature and whether myocardial contrast echo (MCE) is able to detect pharmacol. induced changes in microvascular reflow. Twenty dogs underwent 90 min of LAD occlusion (OCC) followed by 180 min of reperfusion (RP). Five minutes before LAD reopening, an i.v. bolus (5 mg/kg) of LU 135252 was given in 10 dogs and vehicle in the remaining 10. At baseline (BSL), OCC, and 90 and 180 min of RP, microvascular flow (BF) was assessed by microspheres, and MCE was performed with i.v. echo contrast. MCE video intensity and BF were expressed as risk area/control ratio. Myocardial thickness of the risk area was calculated by 2D echo. No differences in BF between the 2 groups were observed at BSL, OCC, and 90 min of RP. At 180 min of RP, BF was decreased in controls (70±7.4% of BSL; P<0.005 vs. BSL) and preserved in LU 135252-treated animals (89±4% of BSL; P=NS vs. BSL; P<0.05 vs. controls). Video intensity at MCE closely followed the changes in BF observed in both groups throughout the protocol. Myocardial thickness at 180 min of RP increased to 138.6±9.9% of BSL in controls and remained at 108.9±7.4% of BSL in treated dogs (P<0.05). Endothelin A-antagonist treatment at the time of reperfusion significantly limited the progressive decrease in postischemic microvascular reflow and the increase in myocardial thickness. MCE allowed a reliable evaluation of pharmacol. induced changes in microvascular flow.
IT **171714-84-4**, LU 135252
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ischemia-reperfusion injury at microvascular level and treatment by endothelin A-selective antagonist and evaluation by myocardial contrast echocardiog.)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

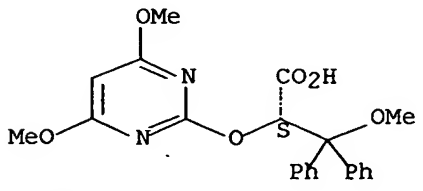
Absolute stereochemistry.



RE.CNT 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 93 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2000:902599 CAPLUS Full-text
DN 134:324649
TI Involvement of the endothelin system in experimental critical hind limb ischemia
AU Luyt, Charles-Edouard; Lepailleur-Enouf, Delphine; Gaultier, Cedric-J.; Valdenaire, Olivier; Steg, Gabriel; Michel, Jean-Baptiste
CS Institut National de la Sante et de la Recherche Medicale, Paris, 75018, Fr.
SO Molecular Medicine (Baltimore, MD, United States) (2000), 6(11), 947-956
CODEN: MOMEF3; ISSN: 1076-1551
PB Johns Hopkins University Press
DT Journal
LA English
AB Endothelin-1 (ET-1) is involved in the pathogenesis of several ischemic diseases. We investigated the hypotheses that ET-1 is involved in the pathogenesis of exptl. critical hind limb ischemia and that ET-1 receptor antagonists have a protective effect. Critical hind limb ischemia was achieved by exclusion of the femoral artery and embolization of collateral vessels in rats. The induction of endothelin system components by ischemia was analyzed by reverse transcription-polymerase chain reaction (RT-PCR) (mRNAs) and immunoassay (peptides) in the plasma and ischemic muscles 5 h (H5), 5 days (D5) and 14 days (D14) after ischemia. Two groups of rats received 100 mg/kg/day of either Bosentan, a mixed ETA/B receptor antagonist (n = 12), or LU 135252, a selective ETA receptor antagonist (n = 9), and a control group without treatment (n = 12) served as control. Muscle blood flow and ischemia were monitored in the ischemic limb by laser Doppler and phosphorylase activity, resp. The procedure induced an 80% decrease in muscle blood flow and complete suppression of phosphorylase activity without necrosis. At day 14, the tissue blood flow remained reduced by 70% and phosphorylase activity was suppressed completely. There was up-regulation of preproendothelin-1, preproET-3, endothelin converting enzyme-1, and ETA. ETB receptor mRNAs in ischemic muscle at day 5 and day 14 was accompanied by an increase in muscle concentration of ET-1 at day 5, without significant changes in plasma endothelin. Treatment with Bosentan and LU 135252 increased tissue blood flow and reduced muscle ischemia at day 14. Tissue production of ET-1 is up-regulated in exptl. critical hind limb ischemia. Inhibition of the endothelin system by a mixed ETA/B receptor antagonist may protect, at least in part, against muscle injury.
IT **171714-84-4**, LU 135252
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(endothelin-1 in pathogenesis of exptl. critical hind limb ischemia and ET-1 receptor antagonists protective effect)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

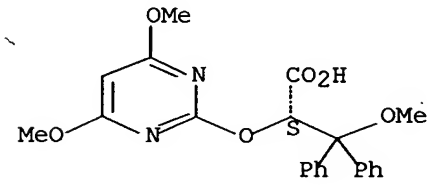
Absolute stereochemistry.



RE.CNT 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

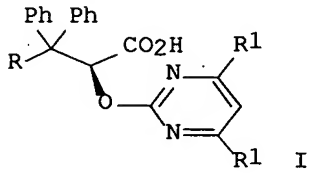
L11 ANSWER 94 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2000:807628 CAPLUS Full-text
DN 134:336098
TI Improvement of renal dysfunction in rats with chronic heart failure after myocardial infarction by treatment with the endothelin A receptor antagonist LU 135252
AU Bauersachs, Johann; Braun, Claude; Fraccarollo, Daniela; Widder, Julian; Ertl, Georg; Schilling, Lothar; Kirchengast, Michael; Rohmeiss, Peter
CS Medizinische Klinik, Universitatsklinikum Mannheim, Mannheim, Germany
SO Journal of Hypertension (2000), 18(10), 1507-1514
CODEN: JOHYD3; ISSN: 0263-6352
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB This work investigated the role of an activated endothelin system in the renal dysfunction observed in chronic heart failure after myocardial infarction. In rats with heart failure after myocardial infarction, and in sham-operated animals, the effect of long-term oral treatment with the selective endothelin A receptor antagonist LU 135252 (30 mg/kg/day) on renal function was investigated. The data demonstrated a restoration of the impaired renal function in chronic ischemic heart failure by treatment with LU 135252. These results offer a promising therapeutic option for the treatment of renal insufficiency in patients with chronic heart failure.
IT **171714-84-4**, LU 135252
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(improvement of renal dysfunction in chronic heart failure after myocardial infarction by treatment with the endothelin A receptor antagonist LU 135252)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 95 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2000:783417 CAPLUS Full-text
DN 134:100825
TI Structural Similarity and Its Surprises: Endothelin Receptor Antagonists - Process Research and Development Report
AU Jansen, R.; Knopp, M.; Amberg, W.; Bernard, H.; Koser, S.; Mueller, S.; Muenster, I.; Pfeiffer, T.; Riechers, H.
CS Hauptlaboratorium, BASF AG, Ludwigshafen, 67056, Germany
SO Organic Process Research & Development (2001), 5(1), 16-22
CODEN: OPRDFK; ISSN: 1083-6160
PB American Chemical Society
DT Journal
LA English
OS CASREACT 134:100825
GI

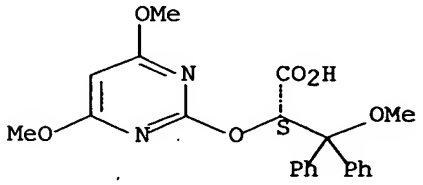


I

AB Process research and pilot plant processes are described for three endothelin (ET) receptor antagonists. The efficient synthesis of the parent compound Darusentan (I, R = R1 = OMe) proceeds via a Darzens reaction from chloroacetate with benzophenone, addition of methanol to the resulting epoxide, saponification of the alkyl propionate and optical resolution of the racemic acid by crystallization with a chiral amine. The final stage of the synthetic sequence involves the introduction of a pyrimidine moiety. Intermediates formed during this process can be used as starting materials for the synthesis of the two other ET receptor antagonists BSF 420627 (I, R = OCH2CH2C6H3(OMe)2-3,4, R1 = Me) and BSF 302146 (I, R = R1 = Me). An ether exchange reaction, which replaces the methoxy with a phenethyloxy substituent, enabled BSF 420627 to be prepared The synthetic route to BSF 302146 employs trimethylaluminum to methylate the epoxide produced by the Darzens reaction.

IT **171714-84-4P**, Darusentan
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of Darusentan analogs)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

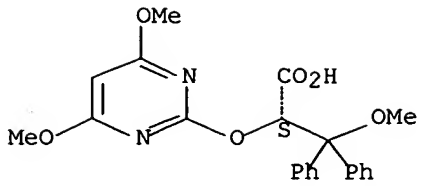
Absolute stereochemistry.



RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 96 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2000:776117 CAPLUS Full-text
DN 134:65992
TI Endothelin-a-receptor antagonist LU 135252 inhibits the formation of ventricular arrhythmias caused by intrapericardial infusion of endothelin-1
AU Kiss, Orsolya; Geller, Laszlo; Merkely, Bela; Szabo, Tamas; Raschack, Manfred; Seres, Leila; Zima, Endre; Juhasz-Nagy, Alexander; Horkay, Ferenc
CS Department of Cardiovascular Surgery, Semmelweis Medical University, Budapest, H-1122, Hung.
SO Journal of Cardiovascular Pharmacology (2000), 36(5, Suppl. 1), S317-S319
CODEN: JCPCDT; ISSN: 0160-2446
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB Intrapericardial endothelin-1 (ET-1) infusion causes dose-dependent severe ventricular arrhythmias. We examined the effects of the endothelin-A- (ETA) receptor antagonist LU 135.252 (LU) on ET-1-induced arrhythmias on six open-chest mongrel dogs. Ten minutes after an i.v. bolus of LU (5 mg/kg), ET-1 (33 pmol/kg/min) was given into the pericardial space for 30 min (LU group). Six dogs received ET-1 infusion without LU treatment (control group). Mean arterial blood pressure (MAP), cardiac output, electrocardiograph (ECG), right ventricular endocardial and epicardial (RVEND, RVEP), and left ventricular endocardial and epicardial (LVEND, LVEP) monophasic action potential durations (MAPDs) were recorded. No significant changes were observed in MAP and cardiac output. MAPD90s did not change significantly in the LU group (basic vs. ET 20 min: RVEP, 186±7 vs. 190±7; LVEP, 189±8 vs. 201±11; RVEND, 191±10 vs. 192±9; LVEND, 199±11 vs. 203±11 ms), while significant MAPD90 prolongation was found in all investigated regions of the control group (ET start vs. ET 20 min: LVEP, 174±3 vs. 208±10*; RVEND, 206±9 vs. 241±12* ms, *$p < 0.05$). No early after-depolarization (EAD) was observed in the LU group, while EADs occurred in three controls. In the LU group, we have not found any significant arrhythmias except nonsustained ventricular tachycardias (nsVTs) in one animal. In the control group incessant nsVTs were observed in six, sustained VTs (sVTs) in four and ventricular fibrillation (VF) in two instances. Significant ST-elevation was observed in all animals in the LU and control groups (LU: 6.7±2.1 mV; control: 10.1±2.0 mV, p = NS). In conclusion, the arrhythmogenic action and the main electrophysiol. effects of pericardial ET-1 infusion, MAPD prolongation and EAD formation, are inhibited by LU. However, LU could not prevent the ischemic changes resulting from ET-1 infusion.
IT **171714-84-4**, LU 135252
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(endothelin-a-receptor antagonist, LU 135252 inhibits formation of ventricular arrhythmias caused by intrapericardial infusion of endothelin-1)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

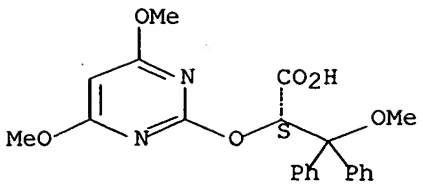
Absolute stereochemistry.



RE.CNT 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 97 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2000:776116 CAPLUS Full-text
DN 134:974
TI The selective endothelin-A-receptor antagonist LU 135.252 inhibits the direct arrhythmogenic action of endothelin-1
AU Merkely, Bela; Szabo, Tamas; Geller, Laszlo; Kiss, Orsolya; Horkay, Ferenc; Raschack, Manfred; Juhasz-Nagy, Alexander
CS Department of Cardiovascular Surgery, Semmelweis Medical University, Budapest, H-1122, Hung.
SO Journal of Cardiovascular Pharmacology (2000), 36(5, Suppl. 1), S314-S316
CODEN: JCPCDT; ISSN: 0160-2446
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB Besides being a strong vasoconstrictor, endothelin-1 (ET-1) also causes severe ventricular arrhythmias. The aim of the authors' study was to differentiate between the vasoconstrictor and arrhythmogenic actions of ET-1 by using the selective endothelin-A-(ETA) receptor antagonist LU 135.252 (LU). A bolus injection of 5 mg/kg LU was administered to 10 anesthetized mongrel dogs in group A. The 30 min intracoronary ET-1 infusion was started 20 min after the LU bolus at a rate of 60 pmol/min. In the control group (group B, n = 8) only ET-1 was administered (60 pmol/min). The left anterior descending coronary artery blood flow (CBF), cardiac output, electrocardiograph (ECG) and arterial blood pressure were monitored. Two monophasic action potential duration (MAPD) catheters were placed onto the left ventricular epicardium (LVEP) and into the right ventricular endocardium (RVEND) to follow electrophysiol. changes. No significant changes were observed in blood pressure (0 min vs. 30 min: group A, 90.0±4.5 vs. 90.0±5.2 mmHg, p = NS; group B, 103±6 vs. 104±3 mmHg, p = NS), cardiac output (0 min vs. 30 min: group A, 3.5±0.7 vs. 3.2±0.8 l/min, p = NS; group B, 3.6±0.4 vs. 3.3±0.3 l/min, p = NS), and MAPD90 (0 min vs. 30 min: group A, LVEP, 241±11 vs. 260±14 ms; RVEND, 233±5 vs. 239±8 ms, p = NS), whereas a significant decrease was observed in CBF (ΔCBF30min: group A, -28±2%, $p < 0.05$; group B, -32±3%, $p < 0.05$). In group A ventricular fibrillation (VF) occurred once. Ventricular premature contractions (VPCs) and short, nonsustained ventricular tachycardias (nsVTs) were observed in seven cases. Early afterdepolarizations and a MAPD90 increase were observed in the control group B (0 min vs. 30 min: LVEP, 244±10 vs. 292±12 ms; RVEND, 255±9 vs. 290±8 ms) accompanied by VPCs, incessant nsVTs. Sustained VT and VF were evident in seven cases. The authors' results indicate, that the applied single bolus injection of LU effectively prevents ET-1-induced major ventricular arrhythmias, whereas it has no effect on coronary vasoconstriction. These data support the notion that ET-1 possesses a direct arrhythmogenic action.
IT **171714-84-4**, LU 135252
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(selective endothelin-A-receptor antagonist LU 135.252 inhibits direct arrhythmogenic action of endothelin-1 in dog)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

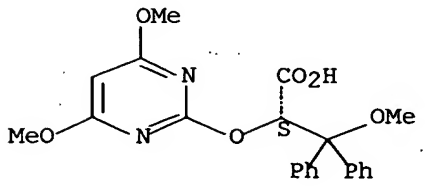
Absolute stereochemistry.



RE.CNT 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 98 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2000:776097 CAPLUS Full-text
DN 134:967
TI Endothelin regulates angiotensin-converting enzyme in the mouse kidney
AU Barton, Matthias; Carmona, Renata; Krieger, Jose E.; Goettsch, Winfried; Morawietz, Henning; D'Uscio, Livius V.; Lattmann, Thomas; Luscher, Thomas F.; Shaw, Sidney
CS Cardiology, University Hospital Zurich and Cardiovascular Research Laboratory, Institute of Physiology, University of Zurich, Switz.
SO Journal of Cardiovascular Pharmacology (2000), 36(5, Suppl. 1), S244-S247
CODEN: JCPCDT; ISSN: 0160-2446
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB Using the orally active endothelin-A- (ETA) receptor antagonist LU135252, the authors determined whether endothelin-1 (ET-1) and/or dietary fat may be involved in angiotensin-converting enzyme (ACE) regulation in vivo. In C57BL6/J mice, renal and pulmonary tissue ACE activity (nmol/l His-Leu/mg protein) was measured and ACE mRNA expression, tissue ET-1 protein content and nitrite/nitrate level were measured in the kidney. Western-type diet increased renal ACE activity by 70% (55±4 vs. 33±3 nmol/l His-Leu/mg protein, $p < 0.05$) and increased renal ET-1 levels (267±19 pg/g vs. 190±18, $p < 0.05$). Chronic LU135252 treatment completely prevented activation of renal ACE activity (13.3±0.3 His-Leu/mg protein nmol/l, $p < 0.05$) independent of ACE mRNA expression or renal ET-1 protein levels. Thus, dietary fat activates renal ACE activity and ET-1 is involved in regulation of tissue ACE activity in vivo independently of ACE mRNA expression.
IT **171714-84-4**, LU135252
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(endothelin regulates angiotensin-converting enzyme in mouse kidney in relation to underlying mechanism)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

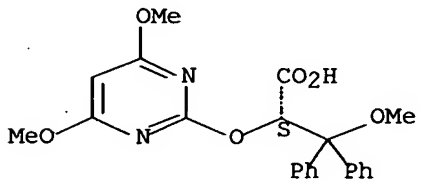
Absolute stereochemistry.



RE.CNT 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 99 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2000:707937 CAPLUS Full-text
DN 134:3451
TI Regulation of the hepatic endothelin system in advanced biliary fibrosis in rats
AU Rothermund, Lars; Leggewie, Stefan; Schwarz, Anja; Thone-Reinecke, Christa; Cho, Jae Jin; Bauer, Christian; Paul, Martin; Neumayer, Hans-H.; Schuppan, Detlef; Hocher, Berthold
CS Medizinische Klinik mit Schwerpunkt Nephrologie der Charite, Humboldt Universitat zu Berlin, Germany
SO Clinical Chemistry and Laboratory Medicine (2000), 38(6), 507-512
CODEN: CCLMFW; ISSN: 1434-6621
PB Walter de Gruyter GmbH & Co. KG
DT Journal
LA English
AB The aim of the present study was to analyze the hepatic endothelin system and its regulation in liver cirrhosis due to bile duct obstruction. Wistar rats were subjected for 6 wk to: (1) sham operation; (2) bile duct obstruction; (3) bile duct obstruction and the selective oral endothelin A receptor antagonist LU 135252; (4) bile duct obstruction and oral silymarin, a hepatoprotective and antifibrotic compound We determined tissue concns. of endothelin-1 and big-endothelin-1 by ELISA and the d. of both endothelin receptor subtypes in plasma membrane fractions by Scatchard anal. The hepatic endothelin system in liver cirrhosis due to chronic bile duct obstruction is characterized by a simultaneous up-regulation of both endothelin-1 tissue concentration (7.2 fold compared to sham operation; $p<0.001$) as well as the d. of both endothelin receptor subtypes (ETA 7.4-fold, ETB 4.9-fold, $p<0.001$, resp.) suggesting a synergistic activation of the hepatic endothelin system in this rat model of non-inflammatory cirrhosis. Treatment with proven antifibrotic agents such as silymarin or a selective endothelin-A-receptor blocker (LU 135252) did not reduce the activity of the hepatic endothelin system, suggesting that the hepatic endothelin system is not activated by the fibrotic process itself.
IT **171714-84-4**, LU 135252
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(regulation of hepatic endothelin system in advanced biliary fibrosis in rats)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

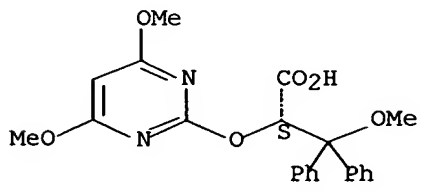
Absolute stereochemistry.



RE.CNT 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 100 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2000:679955 CAPLUS Full-text
DN 134:187957
TI Improved recovery following posttransplant acute renal failure in rat renal isografts with an oral endothelin-A receptor antagonist
AU Braun, Claude; Vetter, Stephan; Conzelmann, Tobias; Schaub, Meike; Kirchengast, Michael; Van Der Woude, Fokko J.; Rohmeiss, Peter
CS Fifth Department of Medicine, University of Heidelberg, Mannheim, D-68167, Germany
SO Experimental Nephrology (2000), 8(4-5), 283-290
CODEN: EXNEEG; ISSN: 1018-7782
PB S. Karger AG
DT Journal
LA English
AB Delayed renal function after transplantation is a strong predictor of long-term graft survival. As an increased expression of endothelin (ET) was demonstrated during ischemia/reperfusion injury, the authors hypothesized that ET-A receptor blockade could improve the recovery of acute renal failure in a rat model of isogenic kidney transplantation. Kidneys of Fisher (F344, RT1lv1) rat donors flushed with cooled University of Wisconsin solution were transplanted into bilaterally nephrectomized Fisher rats. Recipient animals were treated orally either with vehicle or the selective ET-A receptor antagonist LU135252 (30 mg/kg/day p.o.) for 14 days. Unilaterally nephrectomized Fisher rats not subjected to ischemia served as controls. No immunosuppression was given. On days 2, 6, and 14, metabolic studies were performed to evaluate endogenous creatinine clearance, fractional Na excretion, and urinary endothelin excretion. Kidneys were harvested at the end of the experiment for determination of renal ET content and immunohistochem. assessment. Urinary ET excretion was increased in vehicle-treated isografts compared to uninephrectomized controls after 14 days. Treatment with LU135252 resulted in an improvement in creatinine clearance and fractional Na excretion to the level of uninephrectomized rats after 14 days. Isografts treated with selective ET-A receptor blockade demonstrated a marked reduction in cell surface markers for macrophages/monocytes, T cells, MHC-II, and ICAM-1. Treatment with the selective ET-A receptor antagonist LU135252 accelerates recovery of renal function after isogeneic renal transplantation and attenuates cellular graft infiltration. This effect could have major implications for the treatment of patients undergoing renal transplantation, as an improved initial renal function may delay the onset of chronic allograft rejection.
IT **171714-84-4**, LU135252
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)(LU135252 improved recovery following posttransplant acute renal failure)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

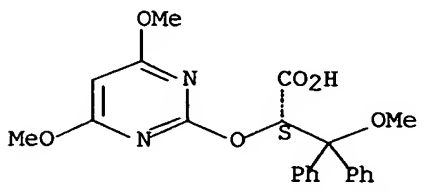
Absolute stereochemistry.



RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 101 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2000:603663 CAPLUS Full-text
DN 133:261492
TI Cardioprotection from ischemia and reperfusion injury by an endothelin A-receptor antagonist in relation to nitric oxide production
AU Gonon, Adrian T.; Gourine, Andrey V.; Pernow, John
CS Department of Cardiology, Karolinska Hospital, Stockholm, S-171 76, Swed.
SO Journal of Cardiovascular Pharmacology (2000), 36(3), 405-412
CODEN: JCPCDT; ISSN: 0160-2446
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB It has previously been shown that endothelin (ET)-receptor antagonists protect the myocardium from ischemia and reperfusion (I/R) injury. The mechanism behind this effect is unclear. The aim of this study was to elucidate the possible interaction between ETA-receptor antagonism and nitric oxide (NO) during I/R. Anesthetized pigs were subjected to 45-min ligation of the left anterior descending coronary artery (LAD) followed by 4 h of reperfusion. Vehicle (n = 7), the ETA-receptor antagonist LU 135252 (LU; 0.1 mg/kg, n = 7), the combination of LU and the NO precursor L-arginine (15 mg/kg, n = 7; LU + L-arg), the NO synthase inhibitor NG-monomethyl-L-arginine (L-NMMA; 0.2 mg/kg, n = 6), or the combination of LU and L-NMMA (LU + L-NMMA; n = 6) were injected into the LAD during the last 10 min of ischemia and the first 5 min of reperfusion. There were no significant differences in coronary flow, pulmonary capillary wedge pressure, mean arterial pressure, or heart rate between the groups before ischemia or at the end of reperfusion. The area at risk was similar in all five groups. The infarct size of the vehicle group was 79 ± 6% of the area at risk. LU and LU + L-arginine (L-arg) reduced the infarct size to 39 ± 6% and 35 ± 8%, resp. ($p < 0.001$ vs. vehicle). L-NMMA completely prevented the infarct-limiting effect of LU. Thus the infarct size in the LU + L-NMMA group was 83 ± 4% ($p < 0.001$ vs. LU alone); L-NMMA did not affect infract size per se (79 ± 4%). ET immunoreactivity increased threefold in the I/R myocardium of the vehicle group. The increase in ET immunoreactivity was significantly attenuated in the LU and LU + L-arg groups ($p < 0.001$), but not in the groups given L-NMMA or LU + L-NMMA. In conclusion, ETA-receptor blockade results in cardioprotection and attenuation of the increase in myocardial ET levels after I/R. Both effects were inhibited by NO synthase blockade, suggesting that they are dependent on maintained production of NO.
IT **171714-84-4**, LU 135252
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)(cardioprotection from ischemia and reperfusion injury by endothelin A receptor antagonist: NO role)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

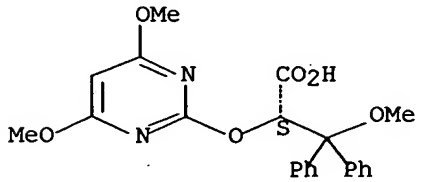
Absolute stereochemistry.



RE.CNT 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 102 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2000:578293 CAPLUS Full-text
DN 133:261289
TI LU135252, an endothelinA receptor antagonist did not prevent pulmonary vascular remodelling or lung fibrosis in a rat model of myocardial infarction
AU Nguyen, Quang Trinh; Colombo, Federico; Rouleau, Jean L.; Dupuis, Jocelyn; Calderone, Angelino
CS Departement de Physiologie, Universite de Montreal and L'Institut de Cardiologie de Montreal, Montreal, QC, H1T 1C8, Can.
SO British Journal of Pharmacology (2000), 130(7), 1525-1530
CODEN: BJPCBM; ISSN: 0007-1188
PB Nature Publishing Group
DT Journal
LA English
AB 1 The early intervention with endothelinA (ETA) receptor antagonists following coronary artery ligation has been shown to reduce the development of pulmonary hypertension, despite a lack of improvement in left ventricular function. 2 The present study examined the contribution of pulmonary vascular remodelling and the progression of lung fibrosis in the development of pulmonary hypertension and the subsequent role of endothelin-1 in these processes in a rat model of myocardial infarction (MI). 3 The administration of 60 mg kg-1 per day of the specific ETA receptor antagonist LU135253 ((+)-(S)-2-(4,6-dimethoxy-pyrimidin-2-yloxy)- 3-methoxy-3,3-diphenyl-propionic acid) 24 h following coronary artery ligation, failed to improve left ventricular contractile indexes, but reduced the extent of pulmonary hypertension, as reflected by the significant decrease in right ventricular systolic pressure. 4 The medial wall thickness of small pulmonary arteries (50-200 μm) was significantly increased 4 wk following MI, albeit LU135253 treatment did not ameliorate this pattern of vascular remodelling. 5 The steady-state mRNA levels of collagen, fibronectin, transforming growth factor-β1, and -β3 were significantly increased in the lungs of MI rats. The treatment with LU135252 did not alter this pattern of gene expression. 6 Thus, these data demonstrate pulmonary vascular remodelling and the increased expression of extracellular matrix proteins represent underlying mechanisms implicated in the development of pulmonary hypertension in the MI rat. 7 Despite the amelioration of the pulmonary hypertensive state, ETA receptor blockade was insufficient to reverse pulmonary vascular remodelling, or the development of lung fibrosis in the MI rat.
IT **171714-84-4**, LU135252
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(endothelinA receptor antagonist LU135252 did not prevent pulmonary vascular remodelling or lung fibrosis in myocardial infarction model)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

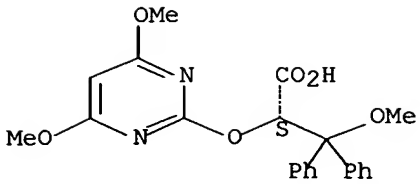
Absolute stereochemistry.



RE.CNT 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 103 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2000:565639 CAPLUS Full-text
DN 133:276726
TI Effect of fluid resuscitation with and without endothelin A receptor blockade on hemoconcentration and organ function in experimental pancreatitis
AU Forgacs, B.; Eibl, G.; Faulhaber, J.; Kahrau, S.; Buhr, H.; Foitzik, T.
CS Department of Surgery II, Semmelweis Medical University, Budapest, Hung.
SO European Surgical Research (2000), 32(3), 162-168
CODEN: EUSRBM; ISSN: 0014-312X
PB S. Karger AG
DT Journal
LA English
AB Intravascular fluid loss contributes to pancreatitis-associated multiple organ dysfunction and is thus a major target for therapy in this life-threatening disease. Studies were carried out to evaluate intravascular fluid loss and extravascular fluid sequestration together with cardiorespiratory and renal function in a well-established rat model of severe acute pancreatitis (AP) and to investigate the effect of fluid resuscitation with and without endothelin receptor A blockade on these parameters. AP was induced in rats by a standardized bile salt infusion into the pancreatic duct and i.v. caerulein hyperstimulation. Six hours after AP induction, animals were randomized into 4 groups to receive (1) no therapy; (2) 4 mL/kg/h Ringer's lactate (RL) i.v.; (3) 8 mL/kg/h RL i.v., or (4) 4 mL/kg/h RL plus an endothelin receptor antagonist. Target parameters measured before and after AP induction and during the 24-h observation period included: mean arterial blood pressure, heart rate, hematocrit, arterial blood gases, urine production, ascites and pleural effusions. After 6 h, all animals presented with severe hemoconcn. (hematocrit >57%) and oliguria (<0.5 mL/6 h). Cardiorespiratory parameters were within the normal range. Up to 12 h after AP induction, animals without therapy had an increased hematocrit and oliguria and developed metabolic acidosis. Animals receiving fluid resuscitation had a significant drop in hematocrit and maintained compensated blood gas values. A significant increase in urine production was only observed in animals given 8 mg/kg/h RL. Between 12 and 24 h, urine production significantly increased with fluid resuscitation and respiratory parameters stabilized except for animals treated with 8 mL/kg/h RL which developed arterial hypoxia and hypercapnia. Intravascular fluid loss and extravascular fluid sequestration together with decreased urine production characterize the early phase of this model of severe AP. Massive fluid resuscitation necessary for increasing urine output may lead to respiratory distress. Reduction of intravascular fluid loss by endothelin receptor blockade is associated with improved renal and respiratory function.
IT **171714-84-4**, LU-135252
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ETA receptor blocker; fluid resuscitation and endothelin A receptor blockade effect on hemoconcn. and organ function in exptl. pancreatitis)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

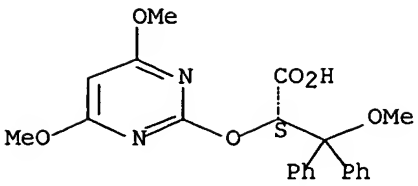
Absolute stereochemistry.



RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 104 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2000:491322 CAPLUS Full-text
DN 133:187774
TI Long-term effects of the endothelinA receptor antagonist LU 135252 and the angiotensin-converting enzyme inhibitor trandolapril on diabetic angiopathy and nephropathy in a chronic type I diabetes mellitus rat model
AU Dhein, Stefan; Hochreuther, Stefan; Spring, Christian Aus Dem; Bollig, Klaus; Hufnagel, Christine; Raschack, Manfred
CS Institute of Pharmacology, University of Halle, Halle, Germany
SO Journal of Pharmacology and Experimental Therapeutics (2000), 293(2), 351-359
CODEN: JPETAB; ISSN: 0022-3565
PB American Society for Pharmacology and Experimental Therapeutics
DT Journal
LA English
AB Diabetic angiopathy is a serious problem in antidiabetic therapy. We wanted to investigate whether treatment with the endothelinA receptor antagonist LU 135252 or with the angiotensin-converting enzyme inhibitor trandolapril might prevent angiopathy in long-term type I diabetes mellitus. Six groups of male Wistar rats were investigated: untreated age-matched control rats, healthy controls treated with trandolapril (0.3 mg/kg), healthy controls treated with LU 135252 (100 mg/kg), untreated diabetic rats, and diabetic rats treated with either trandolapril or LU 135252. Rats were rendered diabetic by injection of streptozotocin. Duration of the disease was 6 mo. Thereafter, rats were sacrificed, and hearts, kidneys, and a mesenterial loop were removed. Hearts and kidneys were processed histol.; the mesenterial loop was perfused with saline at constant pressure for investigation of microvessels using microvideoangiometry while treated with either 30 mM KCl, 1 μM acetylcholine, or 1 μM sodium nitroprusside. All diabetic rats developed hyperglycemia without differences among these three groups. Diabetic rats exhibited marked anemia, which was significantly antagonized by both treatments. The heart capillaries/muscle fibers ratio was decreased significantly in diabetic animals, which was prevented fully by both treatments. Renal glomerular diameter was increased in diabetic rats. This was significantly antagonized by LU 135252 but not by trandolapril. Deposition of homogeneous eosinophilic material within the glomeruli was nearly completely prevented by LU 135252. The acetylcholine-induced vasodilation in mesenteric microvessels was significantly attenuated in diabetic rats, which was significantly antagonized by both treatments. We conclude that both angiotensin and endothelin seem to contribute to the development of diabetic angiopathy and that, in addition to angiotensin-converting enzyme inhibition, blockade of endothelinA receptors may be an interesting new approach to antiangiopathic therapy.
IT **171714-84-4**, LU 135252
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(long-term effects of the endothelinA receptor antagonist LU 135252 and the angiotensin-converting enzyme inhibitor trandolapril on diabetic angiopathy and nephropathy in a chronic type I diabetes mellitus rat model)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

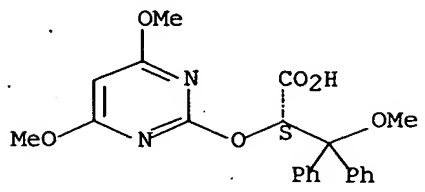
Absolute stereochemistry.



RE.CNT 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 105 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2000:435659 CAPLUS Full-text
DN 133:37941
TI Acute hemodynamic and neurohumoral effects of selective ETA receptor blockade in patients with congestive heart failure
AU Spieker, Lukas E.; Mitrovic, Veselin; Noll, Georg; Pacher, Richard; Schulze, Matthias R.; Muntwyler, Jorg; Schalcher, Christoph; Kiowski, Wolfgang; Luscher, Thomas F.
CS Division of Cardiology, University Hospital, Zurich, Switz.
SO Journal of the American College of Cardiology (2000), 35(7), 1745-1752
CODEN: JACCDI; ISSN: 0735-1097
PB Elsevier Science Inc.
DT Journal
LA English
AB OBJECTIVES: To investigate the hemodynamic effects of the selective endothelin (ET)A receptor antagonist LU135252 in patients with congestive heart failure (CHF). BACKGROUND: Nonselective ETA/B receptor antagonists improve hemodynamics in patients with CHF. Since ETB receptors mediate the release of nitric oxide and the clearance of ET-1, selective ETA antagonists are of special interest. METHODS: The hemodynamic effects of a single oral dose of the selective ETA receptor antagonist LU135252 (1, 10, 30, 100 or 300 mg) were investigated in a multicenter study involving 95 patients with CHF (New York Heart Association II-III) with an ejection fraction ≤35%. RESULTS: Baseline ET-1 pos. correlated with pulmonary vascular resistance, pulmonary capillary wedge pressure (PCWP), and mean pulmonary artery pressure (MPAP, r = 0.37-0.50, p < 0.0004) but were inversely related to cardiac index (CI; r = -0.36, p = 0.0004). LU135252 dose dependently increased CI and decreased mean arterial pressure and systemic vascular resistance (p < 0.03-0.0002), while heart rate remained constant or decreased slightly. Pulmonary capillary wedge pressure, MPAP, pulmonary vascular resistance and right atrial pressure also decreased significantly (p < 0.035-< 0.0001). Two hours after LU135252, plasma ET-1 did not significantly increase after 1 mg but did so by 23% (p = 0.003), 29% (p = 0.0018), 56% (p < 0.0001) and 101% (p < 0.0001) after 10, 30, 100 and 300 mg, resp., while plasma catecholamines remained constant CONCLUSIONS: In patients with CHF, a single oral dose of the selective ETA receptor antagonist LU135252 improves hemodynamics in a dose-dependent manner without activation of other neurohumoral systems and is well tolerated over a wide dose range.
IT **171714-84-4**, LU135252
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(acute hemodynamic and neurohumoral effects of selective ETA receptor antagonist LU135252 in humans with congestive heart failure)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

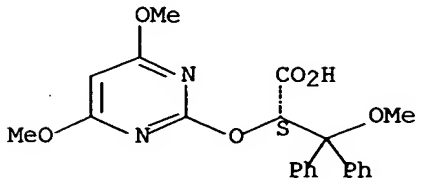
Absolute stereochemistry.



RE.CNT 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 106 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2000:434831 CAPLUS Full-text
DN 133:187767
TI Endothelin-receptor blockade improves endothelial vasomotor dysfunction in heart failure
AU Bauersachs, J.; Fraccarollo, D.; Galuppo, P.; Widder, J.; Ertl, G.
CS Universitatsklinikum Mannheim, II. Medizinische Klinik, Medizinische Klinik der Julius-Maximilians-Universitat Wurzburg, Fakultat fur Klinische Medizin Mannheim der Universitat Heidelberg, Heidelberg, Germany
SO Cardiovascular Research (2000), 47(1), 142-149
CODEN: CVREAU; ISSN: 0008-6363
PB Elsevier Science B.V.
DT Journal
LA English
AB Objectives: To elucidate the effect of selective endothelin ETA- and mixed ETA/B-receptor antagonists on endothelial vasomotor dysfunction in rats with heart failure after myocardial infarction (MI). Methods: Vasoreactivity and superoxide anion formation were determined in aortic rings from Wistar rats 12 wk after extensive MI (>46% of left ventricle) compared to sham-operated animals. Rats were either treated with the selective ETA-receptor antagonist LU 135252 (30 mg/kg/day), the mixed ETA/B-receptor antagonist Bosentan (100 mg/kg/day) or placebo. Results: In MI rats, the concentration-response curve of the endothelium-dependent, nitric oxide-mediated relaxation induced by acetylcholine was significantly shifted to the right and the maximum relaxation was attenuated. Long-term treatment with both ET antagonists significantly improved acetylcholine-induced relaxation in MI rats. LU 135252 was more effective than Bosentan. Endothelium-independent relaxations induced by sodium nitroprusside as well as endothelin- and phenylephrine-induced contractions were similar in all groups of rats. Plasma renin activity and aortic superoxide formation, which were enhanced in rats with heart failure, were normalized by LU 135252, but not by Bosentan treatment. Conclusions: Long-term treatment with ET-receptor antagonists improves endothelial vasomotor dysfunction in rats with chronic MI. This mechanism may essentially contribute to the beneficial effects of ET receptor blockade in heart failure.
IT **171714-84-4**, LU 135252
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(endothelin-receptor blockade improves endothelial vasomotor dysfunction in heart failure)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

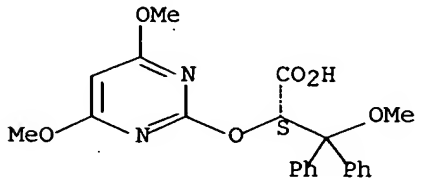
Absolute stereochemistry.



RE.CNT 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 107 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2000:432194 CAPLUS Full-text
DN 133:290930
TI An oral endothelin-A receptor antagonist blocks collagen synthesis and deposition in advanced rat liver fibrosis
AU Cho, Jae-Jin; Hocher, Berthold; Herbst, Hermann; Jia, Ji-Dong; Ruehl, Martin; Hahn, Eckhart G.; Riecken, Ernst Otto; Schuppan, Detlef
CS Department of Gastroenterology, University Hospital Benjamin Franklin, Free University of Berlin, Berlin, Germany
SO Gastroenterology (2000), 118(6), 1169-1178
CODEN: GASTAB; ISSN: 0016-5085
PB W. B. Saunders Co.
DT Journal
LA English
AB Endothelin 1 induces contraction, proliferation, and collagen synthesis of hepatic stellate cells in vitro, which may be mediated via the endothelin A receptor. It is unknown if specific blockade of the endothelin A receptor inhibits hepatic fibrosis in vivo. Groups of 10-20 rats with bile duct occlusion were treated with the nonpeptide endothelin-A receptor antagonist LU 135252 at 80 mg · kg-1 · day-1 from week 1-6 or from week 4-6, or with LU at 10 mg · kg-1 · day-1 from week 1-6. Animals with bile duct occlusion alone and sham-operated rats without or with LU at 80 mg · kg-1 · day-1 over 6 wk served as controls. After 6 wk, parameters of fibrogenesis were determined LU treatment led to improved histol., paralleled by a dose-dependence ≤60% reduction of liver collagen, even when administered at an advanced fibrosis stage. This was accompanied by a decreased mRNA of hepatic procollagen α1(I) and tissue inhibitor of metalloproteinase 1, 2 major effectors of fibrosis, and of serum procollagen type III, a surrogate marker of liver fibrogenesis. Selective endothelin-A receptor blockade can dramatically reduce collagen accumulation in rat 2ndary biliary fibrosis, a model refractory to most potential antifibrotic agents. Endothelin-A receptor antagonists are promising antifibrotic agents in chronic liver disease.
IT **171714-84-4**, LU 135252
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral LU 135252 blocks collagen synthesis and deposition in liver fibrosis)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

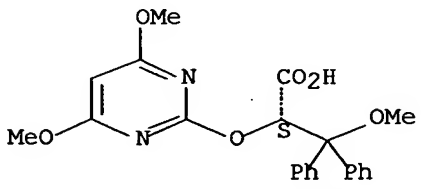
Absolute stereochemistry.



RE.CNT 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 108 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2000:312009 CAPLUS Full-text
DN 133:159792
TI Synergistic effects of AT1 and ETA receptor blockade in a transgenic, angiotensin II-dependent, rat model
AU Bohlender, Jurgen; Gerbaulet, Stephan; Kramer, Jochen; Gross, Michael; Kirchengast, Michael; Dietz, Rainer
CS Franz Volhard Clinic and Max Delbruck Center for Molecular Medicine, Medical Faculty of the Charite, Humboldt University of Berlin, Germany
SO Hypertension (2000), 35(4), 992-997
CODEN: HPRTDN; ISSN: 0194-911X
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB Angiotensin II and endothelin may participate in increasing blood pressure and inducing end-organ damage, but the evidence is conflicting. The authors tested the hypothesis that endothelinA receptor blockade would ameliorate blood pressure and end-organ damage in a rat model of human renin-dependent hypertension. The authors studied rats that were transgenic for both the human renin and angiotensinogen genes. Exptl. groups (n=12 each) of untreated transgenic rats, transgenic rats receiving subdepressor doses of losartan (10 mg/kg), transgenic rats receiving LU 135252 (30 mg/kg), transgenic rats receiving both drugs, and nontransgenic rats were studied between 6 to 10 wk of age. Blood pressure was measured with tail-cuff sphygmomanometry. Gene expression for atrial natriuretic peptide, collagen III, and ACE was measured. The mortality rate in untreated transgenic rats was 42%, which is consistent with previous observations in this line. Single losartan or LU 135252 treatment reduced mortality incidence to 1 rat per group (8%), without lowering blood pressure. In the combination group, blood pressure was normalized and all rats survived. The drug combination also decreased elevated water intake in transgenic rats to normal levels and reduced cardiac hypertrophy. Furthermore, the combination of drugs decreased cardiac atrial natriuretic peptide, ACE gene, and renal collagen III gene expression. The authors suggest that endothelin participates in this model of angiotensin II-induced hypertension and end-organ damage. The authors findings may have clin. implications and provide a rationale for combining angiotensin II type 1 receptor and endothelinA receptor blockade to obtain a synergistic effect.
IT **171714-84-4**, LU 135252
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synergistic effects of AT1 and ETA receptor blockade in angiotensin II-dependent rat model)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

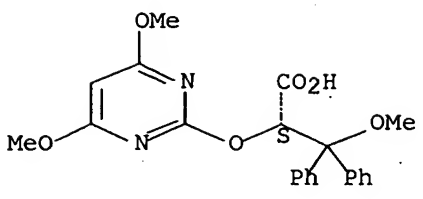
L11 ANSWER 109 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2000:259979 CAPLUS Full-text
DN 132:288794
TI Sympathetic nervous system activity-reducing agents for treatment of disease- or age-related weight loss and for enhancement of exercise performance
IN Anker, Stefan Dietmar; Coats, Andrew Justin Stewart
PA Imperial College Innovations Limited, UK
SO PCT Int. Appl., 72 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000021509	A2	20000420	WO 1999-GB3302	19991015
	WO 2000021509	A3	20001109		
	W: JP, US				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	EP 1121111	A2	20010808	EP 1999-947762	19991015
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 2002527378	T2	20020827	JP 2000-575485	19991015
PRAI	GB 1998-22458	A	19981015		
	GB 1998-22459	A	19981015		
	GB 1999-17181	A	19990723		
	WO 1999-GB3302	W	19991015		

AB A method of treating weight loss due to underlying disease in a patient, the method comprising administering to the patient an effective amount of an agent which reduces sympathetic nervous system activity. A method of treating weight loss due to underlying disease in a patient, the method comprising administering to the patient an effective amount of any one or more of the following: a compound which inhibits the effect of aldosterone such as an aldosterone antagonist; a chymase inhibitor; a cathepsin B inhibitor; a β receptor blocker; an imidazoline receptor antagonist; a centrally acting α receptor antagonist; a peripherally acting α receptor antagonist; a ganglion blocking agent; a drug that has an effect on cardiovascular reflexes and thereby reduces SNS activity such as an opiate; scopolamine; an endothelin receptor antagonist; and a xanthine oxidase inhibitor. The methods are particularly useful in treating cardiac cachexia. The sympathetic nervous system activity-reducing agents may also be used to treat weight loss due to aging and to enhance exercise performance.

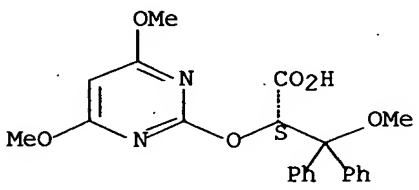
IT **171714-84-4**, LU135252
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (sympathetic nervous system activity-reducing agents for treatment of disease- or age-related weight loss and for enhancement of exercise performance)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.


OMe
N
CO2H
MeO
N
O
S
OMe
Ph
Ph

L11 ANSWER 110 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2000:240304 CAPLUS Full-text
DN 133:12561
TI Endothelium-dependent and -independent vasoreactivity of rat basilar artery in chronic heart failure
AU Widder, Julian; Bauersachs, Johann; Fraccarollo, Daniela; Ertl, Georg; Schilling, Lothar
CS II. Medizinische Klinik, Universitatsklinikum Mannheim, Fakultat fur Klinische Medizin Mannheim der Universitat Heidelberg; and Medizinische Universitatsklinik, Wurzburg, D-97080, Germany
SO Journal of Cardiovascular Pharmacology (2000), 35(4), 515-522
CODEN: JCPCDT; ISSN: 0160-2446
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB Alterations of vasoreactivity are a well-known phenomenon in chronic heart failure (CHF), and activation of the endogenous endothelin (ET) system is suspected to contribute significantly. Regional differences in alterations of vasoreactivity exist; however, nothing is known about cerebrovascular reactivity in CHF. This is of interest in view of increased stroke risk in CHF. Therefore, 12 wk after coronary artery ligation to induce CHF in rats, studies of vasoreactivity of the isolated basilar artery (BA) were performed and compared with third-order branches (MA-A3) and the main trunk (MA) of the superior mesenteric artery. Some of the animals received longterm ET-receptor antagonism by 11 wk of treatment with the selective ETA-receptor antagonist LU 135252 or the mixed ETA/ETB-receptor antagonist bosentan. In rats with CHF, endothelium-dependent relaxation by acetylcholine and A23187 as well as endothelium-independent relaxation by sodium nitroprusside (SNP) was largely unaffected in BA or MA. However, in MA-A3, potency of SNP was diminished without change of maximal effect. ET-1-induced contraction did not differ in arteries from CHF and control rats, either in placebo or ET-receptor antagonist-treated animals. In summary, there was essentially no change of vascular reactivity in similar sized arteries obtained from brain and mesentery. This is in contrast to results on arteries from a variety of vascular regions published previously, thus supporting the concept of organ- and probably time-related changes of vascular function in the development of CHF. The absence of significant alteration of cerebral vasoreactivity may be taken to indicate that changes in cerebral blood flow and increased incidence of ischemic stroke in patients with CHF are caused not by local alterations of vascular function.
IT **171714-84-4**, LU 135252
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(endothelium-dependent and -independent vasoreactivity of rat basilar artery in chronic heart failure)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

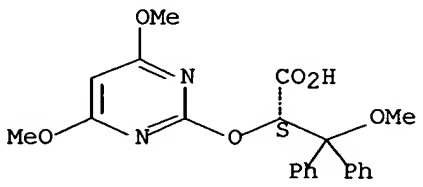
Absolute stereochemistry.



RE.CNT 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 111 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2000:191634 CAPLUS Full-text
DN 133:53023
TI LU-135252, Knoll
AU Spencer, Charles G. C.; Lip, Gregory Y. H.
CS Haemostasis Thrombosis and Vascular Biology Unit, The University of Birmingham, Birmingham, B18 7QH, UK
SO Current Opinion in Cardiovascular, Pulmonary & Renal Investigational Drugs (2000), 2(1), 55-64
CODEN: CCPRFX; ISSN: 1464-8482
PB PharmaPress Ltd.
DT Journal; General Review
LA English
AB A review, with 85 refs., of the pharmacol. of LU-135252, an endothelin A antagonist under development for the potential treatment of congestive heart failure.
IT **171714-84-4P**, LU 135252
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(pharmacol. of endothelin A antagonist LU-135252 for treatment of heart failure)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 86 THERE ARE 86 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 112 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1999:722912 CAPLUS Full-text
DN 131:317804
TI Methods for treatment of pain by inhibiting endothelin-1 action
IN Davar, Gudarz
PA USA
SO PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9956761	A1	19991111	WO 1999-US9732	19990504
	W: AU, CA, JP				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	US 6673832	B1	20040106	US 1998-72428	19980504
	AU 9937849	A1	19991123	AU 1999-37849	19990504
PRAI	US 1998-72428	A	19980504		
	WO 1999-US9732	W	19990504		

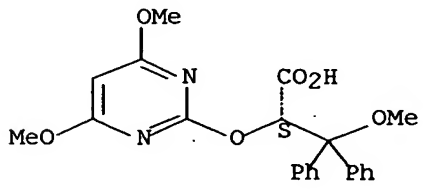
AB A method of determining whether a compound alleviates nerve pain mediated by endothelin-1 (ET-1) involves (i) determining whether the compound has the ability to inhibit a ET-1 action and then (ii) determining whether the compound reduces nerve pain by testing the compound in human patients suffering from pain mediated by the ET-1 action. The invention also includes a method of determining whether a compound alleviates pain caused by nerve injury in human patients by determining the compound ability to inhibit an inflammatory leukocyte response. ET-1 (40-800 μM) applied to rat sciatic nerve in vivo induced direct effect on sensory neurons and pain behavior via a mechanism independent of vasoconstriction of sciatic nerve microvessels. ET-1-induced pain behavior is mediated by ATA subtype of receptor on neurons, as evidenced by using ETA and ETB receptor antagonists, BQ-123 and BQ-788, resp. Therefore, the inhibition of ET-1's vasoconstriction-independent mechanism of causing pain is an effective pain treatment, especially under conditions where ET-1 levels are elevated in a patient, such as metastatic prostate cancer. Furthermore, given that ET-1 acts directly on the sensory neuron ETA receptor, the ETA receptor is an important therapeutic target.

IT **171714-84-4**, LU 135252
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(assay for evaluation of endothelin receptor antagonists for treatment vasoconstriction-independent of pain)

RN 171714-84-4 CAPLUS

CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

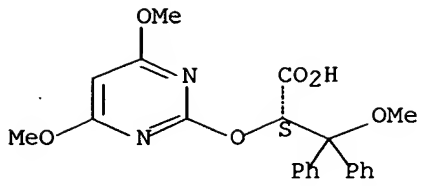
Absolute stereochemistry.



RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 113 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1999:675400 CAPLUS Full-text
DN 132:160978
TI Prevention of chronic renal allograft rejection in rats with an oral endothelin A receptor antagonist
AU Braun, Claude; Conzelmann, Tobias; Vetter, Stephan; Schaub, Meike; Back, Walter E.; Yard, Benito; Kirchengast, Michael; Tullius, Stefan G.; Schnulle, Peter; Van der Woude, Fokko J.; Rohmeiss, Peter
CS V. Department of Medicine (Nephrology/Endocrinology) and Department of Pathology, University Hospital Mannheim, University of Heidelberg, Mannheim, D-68167, Germany
SO Transplantation (1999), 68(6), 739-746
CODEN: TRPLAU; ISSN: 0041-1337
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB Chronic rejection is the most common cause of graft loss in renal transplantation. The pathomechanisms underlying chronic rejection are poorly understood, and no treatment has yet successfully been established. We hypothesized that, in analogy to models of reduced renal mass, the administration of a selective endothelin (ET) A receptor antagonist could improve the course of chronic rejection in renal allografts. Expts. were performed in the Fisher-to-Lewis rat model of chronic rejection. Lewis→Lewis isografts served as controls. Animals were treated with either the oral selective ET-A receptor antagonist LU135252 (50 mg/kg/day) or vehicle. Animal survival, blood pressure, creatinine clearance, proteinuria, and urinary ET excretion were investigated for 24 wk. Kidneys were removed for light microscopical evaluation, determination of ET mRNA expression and tissue protein concentration, and immunohistochem. assessment of cell surface markers. Rats with chronic rejection showed an increase in renal ET mRNA synthesis and ET protein content. Treatment with LU135252 resulted in a significant improvement in survival after 24 wk (0.92 vs. 0.38, $P < 0.01$ by log-rank test). Creatinine clearance was higher in animals treated with the selective ET-A receptor antagonist ($P < 0.05$). LU135252 had no influence on blood pressure and proteinuria. Selective ET-A blockade was associated with significantly less morphol. changes and a significant reduction of expression of cell surface markers for macrophages (ED1), T cells (R73), and MHC II (F17-23-2). The renal ET-A system plays an important role in the pathomechanisms underlying chronic renal allograft rejection, because the treatment with a selective ET-A receptor antagonist dramatically improves the course of chronic renal failure after allograft transplantation. These results offer a novel therapeutical option for treatment of chronic renal allograft rejection, for which so far no therapy is known.
IT **171714-84-4**, LU135252
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prevention of chronic renal allograft rejection in rats with an oral endothelin A receptor antagonist)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

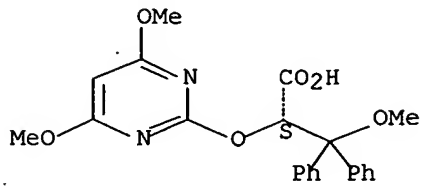
Absolute stereochemistry.



RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 114 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1999:573160 CAPLUS Full-text
DN 132:106297
TI Endothelin ETA receptor blockade prevents the progression of renal failure and hypertension in uraemic rats
AU Brochu, Edith; Lacasse-M., Sonia; Moreau, Claudia; Lebel, Marcel; Kingma, Iris; Grose, John H.; Lariviere, Richard
CS Research Centre and Division of Nephrology, CHUQ, L'Hotel-Dieu de Quebec Hospital and Department of Medicine, Laval University, Quebec, QC, Can.
SO Nephrology, Dialysis, Transplantation (1999), 14(8), 1881-1888
CODEN: NDTREA; ISSN: 0931-0509
PB Oxford University Press
DT Journal
LA English
AB Background. Elevated plasma and urine endothelin-1 (ET-1) levels have been reported in renal failure and may be involved in renal disease progression. We investigated whether these changes are related to increased vascular and renal ET-1 production in the pole resection remnant kidney model of chronic renal failure in the rat. Methods. Uremic Wistar rats were prepared by surgical renal mass 5/6 ablation and compared with sham-operated controls (protocol 1). Immunoreactive-ET-1 (ir-ET-1) concentration was measured by radio-immunoassay after sample extraction and purification To investigate the functional role of ET-1 during the progression of chronic renal failure, uremic rats (protocol 2) were treated with either the vehicle or the ET-1 type A (ETA) receptor antagonist LU135252 (LU). Results. Systolic blood pressure and serum creatinine, as well as urinary volume and proteinuria, were significantly higher, whereas creatinine clearance was reduced in uremic rats compared with sham-operated controls. As expected, plasma and urine ir-ET-1 concns. were increased in uremic rats ($P<0.01$) and were related to the increased ir-ET-1 levels in blood vessels and glomeruli ($P<0.01$). Pos. correlation was found between plasma, thoracic aorta and mesenteric arterial bed ir-ET-1 levels and systolic blood pressure, as well as blood vessel hypertrophy. In addition, increased urinary ir-ET-1 excretion correlated with the rise in serum creatinine and proteinuria. In protocol 2, a 3-wk treatment period with LU was initiated once uremia and hypertension were established. In untreated uremic rats, systolic blood pressure increased further ($P<0.05$), but this was not the case in LU-treated uremic rats. At the end of treatment, serum creatinine and proteinuria were significantly lower ($P<0.05$) and creatinine clearance was higher ($P<0.01$) in LU-treated rats compared with uremic-untreated animals. While plasma ir-ET-1 concentration was similar in the two groups, ir-ET-1 concentration in thoracic aorta, mesenteric arterial bed, renal cortex and urine was significantly lower in LU-treated animals ($P<0.01$). In addition, heart, thoracic aorta and mesenteric arterial wet weight to body weight ratios were also significantly reduced in LU-treated uremic rats ($P<0.05$). Conclusions. Elevated plasma ET-1 concentration and urinary ET-1 excretion in rats with renal mass ablation are related to enhanced ET-1 production in vascular and renal tissues, thus suggesting an important role for ET-1 in the aggravation of hypertension and vascular hypertrophy as well as in the progression of renal insufficiency. These pathophysiol. effects are prevented by treatment with selective ETA receptor blockade.
IT **171714-84-4**, LU135252
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(role of endothelin-1 in the aggravation of hypertension and the progression of renal failure)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

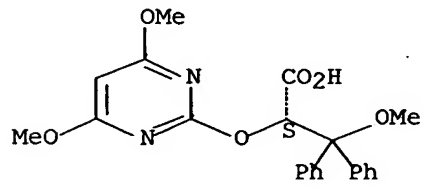
Absolute stereochemistry.



RE.CNT 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 115 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1999:547063 CAPLUS Full-text
DN 131:266799
TI Altered endothelin-1 binding following balloon angioplasty of pig coronary arteries: effect of the ETA receptor antagonist, LU 135252
AU Dashwood, Michael R.; Noertersheuser, Peter; Kirchengast, Michael; Munter, Klaus
CS Departnent of Chemical Pathology and Human Metabolism, Royal Free Hospital School of Medicine, London, NW3 2PF, UK
SO Cardiovascular Research (1999), 43(2), 445-456
CODEN: CVREAU; ISSN: 0008-6363
PB Elsevier Science B.V.
DT Journal
LA English
AB Objective: Since raised levels of endothelin-1 (ET-1) have been detected in the human coronary sinus following percutaneous transluminal angioplasty (PTCA) we investigated the role of ET-1 in the etiol. of vascular restenosis. Methods: Balloon angioplasty of coronary arteries was performed in pigs and the animals were treated with placebo or the endothelin (ETA) receptor antagonist LU 135252 (30 mg/kg/day). After 4 wk vascular stenosis and the distribution of endothelin and its receptors was evaluated. Results: The pronounced neointima formation in the control group (neointima:media ratio=0.87±0.36) was significantly reduced by LU 135252 (0.43±0.30, P<0.001). Angioplasty caused a significant increase in medial ETA (approx. 275%, P<0.026) and ETB (approx. 250%, P<0.001) binding to injured, compared with non-injured segments, an effect that was also reduced by LU 135252 (ETA =11.5% increase; ETB= 14% increase). The neointima of control animals exhibited ET-1 like immunoreactivity as well as ETA and ETB binding sites. Conclusion: These data indicate that endothelin is locally-released from endothelial and vascular smooth muscle cells following angioplasty which binds to ETA and ETB receptor sites in the neointima and media. Since administration of the ETA antagonist LU 135252 markedly reduces neointima formation and medial ET binding, we conclude that vascular smooth muscle cell proliferation and subsequent neointima formation is mediated predominantly via ETA receptors. These data underscore the therapeutic potential of ETA antagonists in reducing the degree of restenosis following vascular injury.
IT **171714-84-4**, LU 135252
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(altered endothelin-1 binding following balloon angioplasty of pig coronary arteries and effect of the ETA receptor antagonist, LU 135252)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 116 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1999:538136 CAPLUS Full-text
DN 131:165311
TI New carboxylic acid derivatives with 5-substituted pyrimidine ring, their preparation and use as endothelin receptor antagonists
IN Amberg, Wilhelm; Jansen, Rolf; Kling, Andreas; Klinge, Dagmar; Riechers, Hartmut; Hergenroeder, Stefan; Raschack, Manfred; Unger, Liliane
PA BASF A.-G., Germany
SO Ger. Offen., 20 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 19806438	A1	19990819	DE 1998-19806438	19980217
	CA 2321182	AA	19990826	CA 1999-2321182	19990205
	WO 9942453	A1	19990826	WO 1999-EP776	19990205
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	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
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	BR 9907911	A	20001024	BR 1999-7911	19990205
	TR 200002376	T2	20001221	TR 2000-200002376	19990205
	EP 1066268	A1	20010110	EP 1999-911657	19990205
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, FI, RO				
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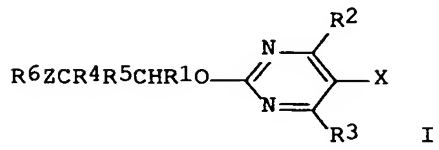
	TW 579376	B	20040311	TW 1999-88102031	19990210
	ZA 9901214	A	20000816	ZA 1999-1214	19990216
	BG 104577	A	20010330	BG 2000-104577	20000704
	NO 2000004075	A	20000815	NO 2000-4075	20000815
	HR 2000000602	A1	20010630	HR 2000-602	20000913
PRAI	DE 1998-19806438	A	19980217		
	WO 1999-EP776	W	19990205		

OS MARPAT 131:165311
GI



I

AB The title compds. [I; R1 = tetrazolyl, C(O)R; R = OR7, (substituted) N-linked 5-membered heteroarom. residue, O(CH2)pS(:O)kR8, NHSO2R9; R7 = H, cation, (substituted) C3-8 cycloalkyl, (substituted) C1-8 alkyl, (substituted) Ph, (substituted) CH2Ph, C3-6 (halo)alkenyl, C3-6 (halo)alkynyl; R8, R9 = (substituted) C1-4 alkyl, (substituted) C3-8 cycloalkyl, (substituted) C3-6 alkenyl, (substituted) C3-6 alkynyl, (substituted) Ph; k = 0-2; p = 1-4; R2, R3 = H, OH, (substituted) amino, halo, alkyl, alkenyl, alkynyl, hydroxyalkyl,

haloalkyl, alkoxy, etc.; R4, R5 = (substituted) Ph, (substituted) naphthyl, C3-7 cycloalkyl, etc.; R6 = H, (substituted) C1-8 alkyl, (substituted) C3-6 alkenyl, (substituted) C3-6 alkynyl, (substituted) C3-8 cycloalkyl, (substituted) Ph, (substituted) naphthyl, (substituted) 5- or 6-membered heteroarom. residue; X = halo, C1-4 haloalkyl, OH; Z = O, S, single bond], their enantiomers, diastereomers, and physiol. compatible salts are useful as endothelin receptor antagonists for treatment of diseases associated with elevated endothelin levels, such as chronic cardiac insufficiency, restenosis, hypertension, acute or chronic kidney failure, cerebral ischemia, asthma, benign prostate hyperplasia, and prostate cancer. Thus, Me 2-hydroxy-3-methoxy-3,3-diphenylpropionate reacted with NaH and 4,6-dimethoxy-5-fluoro-2-methylsulfonylpyrimidine in DMF to produce I (R1 = CO2Me, R2 = R3 = OMe, R4 = R5 = Ph, R6 = Me, X = F, Z = O), which was saponified to the corresponding acid (R1 = CO2H) (II). II bound to endothelin ETA and ETB receptors with Ki 7.4 and 1200 nM, resp.

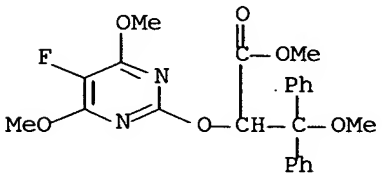
IT **238752-47-1P 238752-48-2P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(carboxylic acid derivs. with substituted pyrimidine ring, their preparation and use as endothelin receptor antagonists)

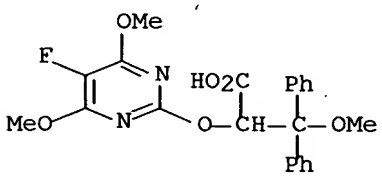
RN 238752-47-1 CAPLUS

CN Benzenepropanoic acid, α-[(5-fluoro-4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, methyl ester (9CI) (CA INDEX NAME)



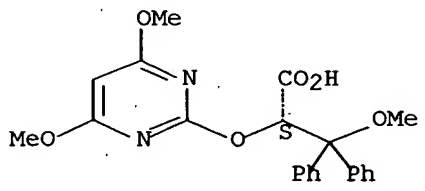
RN 238752-48-2 CAPLUS

CN Benzenepropanoic acid, α-[(5-fluoro-4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl- (9CI) (CA INDEX NAME)



L11 ANSWER 117 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1999:438103 CAPLUS Full-text
DN 131:193969
TI Nonpeptide endothelin receptor antagonists attenuate the pressor effect of diaspirin-crosslinked hemoglobin in rat
AU Rioux, Francis; Harvey, Nathalie; Moisan, Steve; Lariviere, Richard; Lebel, Marcel; Grose, John H.; Burhop, Kenneth
CS Centre de recherche (Universite Laval), Hotel-Dieu de Quebec, Quebec, QC, G1R 2J6, Can.
SO Canadian Journal of Physiology and Pharmacology (1999), 77(3), 188-194
CODEN: CJPPA3; ISSN: 0008-4212
PB National Research Council of Canada
DT Journal
LA English
AB Endothelin 1 (ET-1) is a potent vasoactive and mitogenic peptide that is thought to participate in the hemodynamic effects elicited by drugs that block the biosynthesis and release of endothelium-derived nitric oxide (NO), such as NO synthase inhibitors. Using the nonpeptide endothelin receptor antagonists bosentan and LU-135252, we tested the hypothesis that endothelins contribute to the pressor activity of diaspirin-crosslinked Hb (DCLHb), a Hb-based oxygen carrier, whose pressor activity in mammals is attributed primarily to a scavenging action towards NO. The NO synthase inhibitor nitro-L-arginine Me ester (L-NAME), ET-1, and noradrenaline (NA) were used as reference drugs. Bosentan markedly reduced the pressor effects elicited by DCLHb, L-NAME, and ET-1, but not those evoked by NA. LU-135252 attenuated the pressor effect elicited by DCLHb and ET-1, but not that produced by L-NAME or NA. The decreases in heart rate associated with the pressor effect of DCLHb and L-NAME were reduced by LU-135252, whereas only those elicited by DCLHb were attenuated by bosentan. In contrast with bosentan, LU-135252 caused a decrease in the baseline blood pressure and heart rate. These results suggest that endothelins may participate in the pressor activity of DCLHb. They suggest also that nonpeptide endothelin receptor antagonists such as bosentan or LU-135252 may be useful to counteract endothelin-mediated undesirable hemodynamic effects of drugs that inhibit the activity of the NO system.
IT **171714-84-4**, LU-135252
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nonpeptide endothelin receptor antagonists attenuate the pressor effect of diaspirin-crosslinked Hb in rat)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)-, (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 118 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1999:381011 CAPLUS Full-text
DN 131:23542
TI Obesity treatment with endothelin receptor antagonists
IN Muenter, Klaus; Kirchengast, Michael
PA Knoll A.-G. Chemische Fabriken, Germany
SO Ger. Offen., 4 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 19754082	A1	19990610	DE 1997-19754082	19971205
	CA 2311423	AA	19990617	CA 1998-2311423	19981121
	WO 9929308	A2	19990617	WO 1998-EP7501	19981121
	WO 9929308	A3	19990930		
	W: AL, AU, BG, BR, BY, CA, CN, CZ, GE, HU, ID, IL, JP, KR, KZ, LT, LV, MK, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, US, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	AU 9921535	A1	19990628	AU 1999-21535	19981121
	AU 751053	B2	20020808		
	EP 1035851	A2	20000920	EP 1998-965685	19981121
	EP 1035851	B1	20010816		
	R: AT, BE, CH, DE, ES, FR, GB, IT, LI, NL, SE, FI				
	BR 9815335	A	20001017	BR 1998-15335	19981121
	AT 204172	E	20010915	AT 1998-965685	19981121
	ES 2162493	T3	20011216	ES 1998-965685	19981121
	JP 2002512173	T2	20020423	JP 2000-523980	19981121
	US 6197780	B1	20010306	US 2000-530131	20000427
	NO 2000002777	A	20000602	NO 2000-2777	20000530
	HK 1037141	A1	20050225	HK 2001-107896	20011109
PRAI	DE 1997-19754082	A	19971205		
	WO 1998-EP7501	W	19981121		

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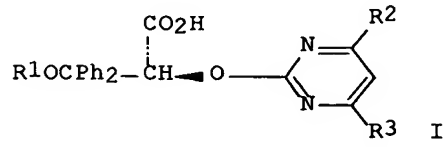


I

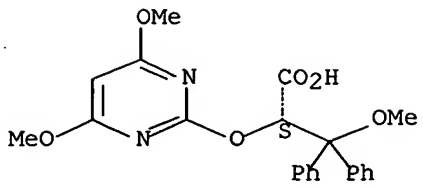
AB Compns. containing endothelinA and mixed endothelinA/B receptors are provided for treatment of obesity. Thus, in mice lacking the gene for apolipoprotein E which were fed a fatty diet (a model for obesity in humans), administration of pyrimidinol derivative I [R1 = 3,4- (MeO)2C6H3CH2CH2, R2 = R3 = Me] (50 mg/kg/day) completely prevented gains in body and liver weight Coated tablets were prepared containing I (R1 = Me, R2 = R3 = OMe) 300.0, lactose 30.0, microcryst. cellulose 30.0, PVP 20.0, Mg stearate 5.0, PEG-6000 0.8, yellow Fe oxide 1.2, TiO2 0.3, and talc 0.7 mg.

IT **171714-84-4**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(obesity treatment with endothelin receptor antagonists)

RN 171714-84-4 CAPLUS

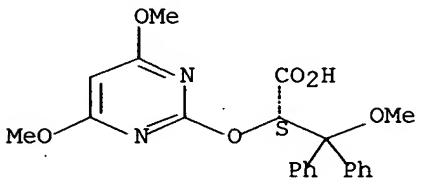
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L11 ANSWER 119 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1999:358127 CAPLUS Full-text
DN 131:153314
TI Pharmacology of the endothelinA receptor antagonist: LU 135252
AU Rohmeiss, P.; Birck, R.; Braun, C.; Munter, K.; Van Der Woude, F. J.; Kirchengast, M.
CS Fifth Department of Medicine, University Hospital Mannheim, University of Heidelberg, Mannheim, Germany
SO Cardiovascular Drug Reviews (1998), 16(4), 391-412
CODEN: CDREEA; ISSN: 0897-5957
PB Neva Press
DT Journal; General Review
LA English
AB A review, with 85 refs., on pharmacol. of a propionic acid derivative, LU 135252, as a selective antagonist of endothelinA receptors. (1) Mechanism of action, (2) effects in congestive heart failure, hypertension, acute and chronic renal failure, restenosis, arteriosclerosis, and acute pancreatitis, and (3) future outlook and clin. perspectives are discussed.
IT **171714-84-4**, LU 135252
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacol. of endothelinA receptor antagonist LU 135252)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

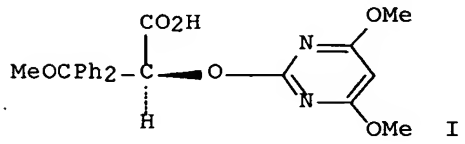


RE.CNT 85 THERE ARE 85 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 120 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1999:249160 CAPLUS Full-text
DN 130:287082
TI Combined pharmaceutical formulations for treatment of cardiovascular disorders
IN Muenter, Klaus; Kirchengast, Michael; Hergenroeder, Stefan
PA Knoll A.-G. Chemische Fabriken, Germany
SO Ger. Offen., 4 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI DE 19744799	A1	19990415	DE 1997-19744799	19971010
PRAI DE 1997-19744799		19971010		

GI



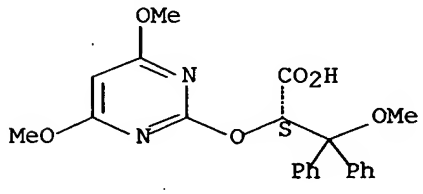
I

AB Combinations of an endothelin antagonist (e.g. pyrimidine derivative I) and a diuretic show synergistic activity in treatment of hypertension, coronary artery disease, cardiac or renal insufficiency, renal or myocardial ischemia, subarachnoid hemorrhage, Raynaud's disease, and peripheral arterial occlusion. Thus, tablets containing I 100.0, furosemide 150.0, anhydrous lactose 30.0, microcryst. cellulose 30.0, PVP 20.0, and Mg stearate 5.0 mg were coated with a mixture of PEG 6000 0.8, yellow Fe oxide 1.2, TiO2 0.3, and talc 0.7 mg.

IT **171714-84-4**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combined pharmaceutical formulations for treatment of cardiovascular disorders)

RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

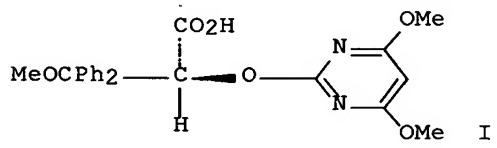
Absolute stereochemistry.



L11 ANSWER 121 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1999:238539 CAPLUS Full-text
DN 130:272031
TI Method for suppressing transplant rejection with endothelin receptor antagonists
IN Kirchengast, Michael; Muenter, Klaus
PA Knoll A.-G. Chemische Fabriken, Germany
SO Ger. Offen., 4 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 19743681	A1	19990408	DE 1997-19743681	19971002
	WO 9917756	A2	19990415	WO 1998-EP6281	19981002
	WO 9917756	A3	19990729		
	W: AL, AU, BG, BR, BY, CA, CN, CZ, GE, HU, ID, IL, JP, KR, KZ, LT, LV, MK, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, US, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	AU 9917529	A1	19990427	AU 1999-17529	19981002
PRAI	DE 1997-19743681	A	19971002		
	WO 1998-EP6281	W	19981002		

GI



I

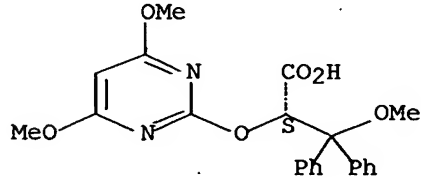
AB Rejection of transplanted organs is inhibited by administration of endothelin A and/or endothelin A/B receptor antagonists such as pyrimidine derivative I systemically at 50-500 mg/day throughout the lifetime of the transplant. Thus, capsules were prepared each containing I 250, lactose 18.0, PVP 15.0, microcryst. cellulose 17.5, Na carboxymethylstarch 10.0, talc 0.7, and Mg stearate 3.0 mg.

IT **171714-84-4**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method for suppressing transplant rejection with endothelin receptor antagonists)

RN 171714-84-4 CAPLUS

CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

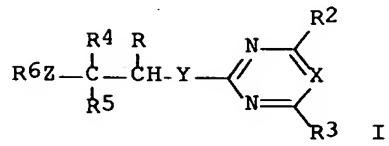
Absolute stereochemistry.



L11 ANSWER 122 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1999:234126 CAPLUS Full-text
DN 130:257367
TI Multicomponent pharmaceutical formulations for treatment of vasoconstrictive disorders
IN Kirchengast, Michael; Muenter, Klaus
PA Knoll A.-G. Chemische Fabriken, Germany
SO Ger. Offen., 34 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 19743143	A1	19990401	DE 1997-19743143	19970930
	CA 2304698	AA	19990408	CA 1998-2304698	19980910
	WO 9916444	A1	19990408	WO 1998-EP5772	19980910
	W: AL, AU, BG, BR, BY, CA, CN, CZ, GE, HU, ID, IL, JP, KR, KZ, LT, LV, MK, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, US, AM, AZ, KG, MD, TJ, TM				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	AU 9892672	A1	19990423	AU 1998-92672	19980910
	AU 739860	B2	20011025		
	EP 1019055	A1	20000719	EP 1998-945323	19980910
	EP 1019055	B1	20030507		
	R: AT, BE, CH, DE, ES, FR, GB, IT, LI, NL, SE, FI				
	BR 9812404	A	20000919	BR 1998-12404	19980910
	JP 2001517703	T2	20011009	JP 2000-513580	19980910
	AT 239479	E	20030515	AT 1998-945323	19980910
	RU 2213577	C2	20031010	RU 2000-111500	19980910
	ES 2199461	T3	20040216	ES 1998-945323	19980910
	US 6352992	B1	20020305	US 2000-508989	20000320
	NO 2000001634	A	20000329	NO 2000-1634	20000329
	NO 319048	B1	20050606		
	HK 1032355	A1	20050304	HK 2001-102973	20010425
PRAI	DE 1997-19743143	A	19970930		
	WO 1998-EP5772	W	19980910		

OS MARPAT 130:257367
GI



I

AB Novel combinations of an endothelin antagonist and a β-receptor blocker are provided for treatment of vasoconstrictive disorders. The endothelin antagonist is a pyrimidine- or triazine-substituted carboxylic acid [I; R = CHO, CN, CO2H, tetrazolyl, etc.; R2, R3 = H, OH, amino, halo, C1-4 alkyl, haloalkyl, alkoxy, etc.; R4, R5 = (substituted) Ph or naphthyl, C3-7 cycloalkyl; R6 = H, (substituted) alkyl, alkenyl, alkynyl, or cycloalkyl; X = N, CR14; R14 = H, C1-5 alkyl; or R14CCR3 = 5- or 6-membered ring; Y = O, S, single bond; Z = O, S, SO, SO2, single bond] or related compound Thus, hard gelatin capsules were filled with I (R = CO2H, R2 = R3 = OMe, R4 = R5 = Ph, R6 = Me, X = CH, Y = Z = O) 100.0, bucindolol 30.0, lactose 18.0, PVP 15.0, microcryst. cellulose 17.5, Na carboxymethylstarch 10.0, talc 9.0, and Mg stearate 3.0 mg.

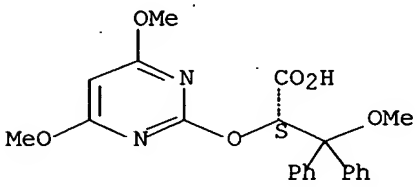
IT **171714-84-4**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(multicomponent pharmaceutical formulations for treatment of vasoconstrictive disorders)

RN 171714-84-4 CAPLUS

CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)-. (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L11 ANSWER 123 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1999:234125 CAPLUS Full-text
DN 130:257366
TI Multicomponent pharmaceutical formulations for treatment of cardiovascular disorders
IN Muenter, Klaus; Kirchengast, Michael; Hergenroeder, Stefan
PA Knoll A.-G. Chemische Fabriken, Germany
SO Ger. Offen., 34 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 19743142	A1	19990401	DE 1997-19743142	19970930
	WO 9916446	A1	19990408	WO 1998-EP5916	19980917
	W: AL, AU, BG, BR, BY, CA, CN, CZ, GE, HU, ID, IL, JP, KR, KZ, LT, LV, MK, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, US, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	AU 9897447	A1	19990423	AU 1998-97447	19980917
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OS MARPAT 130:257366
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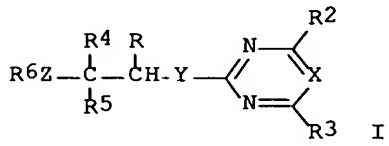


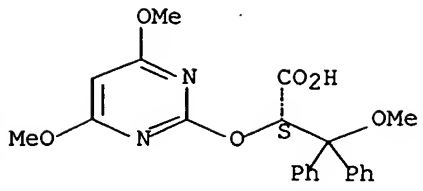
I

AB Novel combinations of an endothelin antagonist and a calcium antagonist are provided for treatment of cardiovascular disorders. The endothelin antagonist is a pyrimidine- or triazine-substituted carboxylic acid [I; R = CHO, CN, CO2H, tetrazolyl, etc.; R2, R3 = H, OH, amino, halo, C1-4 alkyl, haloalkyl, alkoxy, etc.; R4, R5 = (substituted) Ph or naphthyl, C3-7 cycloalkyl; R6 = H, (substituted) alkyl, alkenyl, alkynyl, or cycloalkyl; X = N, CR14; R14 = H, C1-5 alkyl; or R14CCR3 = 5- or 6-membered ring; Y = O, S, single bond; Z = O, S, SO, SO2, single bond] or related compound Thus, hard gelatin capsules were filled with I (R = CO2H, R2 = R3 = OMe, R4 = R5 = Ph, R6 = Me, X = CH, Y = Z = O) 100.0, gallopamil 75.0, lactose 18.0, PVP 15.0, microcryst. cellulose 17.5, Na carboxymethylstarch 10.0, talc 9.0, and Mg stearate 3.0 mg.

IT **171714-84-4**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(multicomponent pharmaceutical formulations for treatment of cardiovascular disorders)

RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

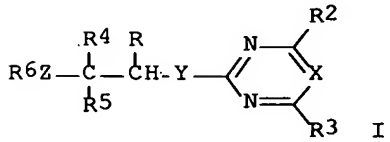
Absolute stereochemistry.


OMe
N
CO2H
OMe
MeO
N
O
S
Ph
Ph

L11 ANSWER 124 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1999:234124 CAPLUS Full-text
DN 130:257365
TI Multicomponent pharmaceutical formulations for treatment of kidney failure
IN Hahn, Alfred; Kirchengast, Michael; Muenter, Klaus
PA Knoll A.-G. Chemische Fabriken, Germany
SO Ger. Offen., 34 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 19743141	A1	19990401	DE 1997-19743141	19970930
	CA 2304712	AA	19990408	CA 1998-2304712	19980910
	WO 9916445	A1	19990408	WO 1998-EP5773	19980910
	W: AL, AU, BG, BR, BY, CA, CN, CZ, GE, HU, ID, IL, JP, KR, KZ, LT, LV, MK, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, US, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	AU 9895395	A1	19990423	AU 1998-95395	19980910
	AU 750755	B2	20020725		
	EP 1014989	A1	20000705	EP 1998-948954	19980910
	EP 1014989	B1	20040114		
	R: AT, BE, CH, DE, ES, FR, GB, IT, LI, NL, SE, FI				
	JP 2001517704	T2	20011009	JP 2000-513581	19980910
	AT 257706	E	20040115	AT 1998-948954	19980910
	ES 2214734	T3	20040916	ES 1998-948954	19980910
	US 6329384	B1	20011211	US 2000-508993	20000320
	NO 2000001548	A	20000324	NO 2000-1548	20000324
PRAI	DE 1997-19742717	A	19970926		
	DE 1997-19743141	A	19970930		
	WO 1998-EP5773	W	19980910		

OS MARPAT 130:257365
GI



I

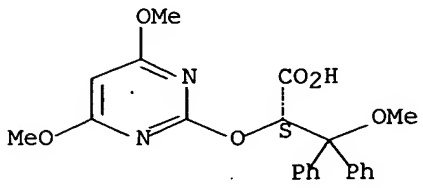
AB Novel combinations of an endothelin antagonist and an ACE inhibitor are provided for treatment of kidney failure. The endothelin antagonist is a pyrimidine- or triazine-substituted carboxylic acid [I; R = CHO, CN, CO2H, tetrazolyl, etc.; R2, R3 = H, OH, amino, halo, C1-4 alkyl, haloalkyl, alkoxy, etc.; R4, R5 = (substituted) Ph or naphthyl, C3-7 cycloalkyl; R6 = H, (substituted) alkyl, alkenyl, alkynyl, or cycloalkyl; X = N, CR14; R14 = H, C1-5 alkyl; or R14CCR3 = 5- or 6-membered ring; Y = O, S, single bond; Z = O, S, SO, SO2, single bond] or related compound Thus, hard gelatin capsules were filled with I (R = CO2H, R2 = R3 = OMe, R4 = R5 = Ph, R6 = Me, X = CH, Y = Z = O) 100.0, ramipril 2.5, lactose 18.0, PVP 15.0, microcryst. cellulose 17.5, Na carboxymethylstarch 10.0, talc 9.0, and Mg stearate 3.0 mg.

IT **171714-84-4**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(multicomponent pharmaceutical formulations for treatment of kidney failure)

RN 171714-84-4 CAPLUS

CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

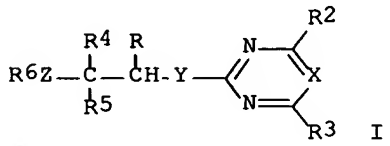
Absolute stereochemistry.



L11 ANSWER 125 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1999:234123 CAPLUS Full-text
DN 130:257364
TI Multicomponent pharmaceutical formulations for treatment of cardiovascular disorders
IN Muenter, Klaus; Kirchengast, Michael; Klein, Gisela; Korioth, Horst
PA Knoll A.-G. Chemische Fabriken, Germany
SO Ger. Offen., 34 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI DE 19743140	A1	19990401	DE 1997-19743140	19970930
PRAI DE 1997-19743140		19970930		

OS MARPAT 130:257364
GI



I

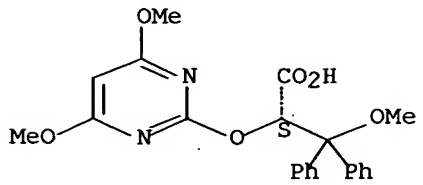
AB Novel combinations of an endothelin antagonist and a vasodilator are provided for treatment of cardiovascular disorders. The endothelin antagonist is a pyrimidine- or triazine-substituted carboxylic acid [I; R = CHO, CN, CO2H, tetrazolyl, etc.; R2, R3 = H, OH, amino, halo, C1-4 alkyl, haloalkyl, alkoxy, etc.; R4, R5 = (substituted) Ph or naphthyl, C3-7 cycloalkyl; R6 = H, (substituted) alkyl, alkenyl, alkynyl, or cycloalkyl; X = N, CR14; R14 = H, C1-5 alkyl; or R14CCR3 = 5- or 6-membered ring; Y = O, S, single bond; Z = O, S, SO, SO2, single bond] or related compound Thus, administration of a combination of I (R = CO2H, R2 = R3 = OMe, R4 = R5 = Ph, R6 = Me, X = CH, Y = Z = O) (II) and hydralazine (5 and 0.5 mg/kg, resp.) orally to normal male beagles synergistically decreased their mean arterial pressure after 2 h by 15.4 mm Hg. Hard gelatin capsules were prepared containing II 200.0, hydralazine 50.0, lactose 18.0, PVP 15.0, microcryst. cellulose 17.5, Na carboxymethylstarch 10.0, talc 9.0, and Mg stearate 3.0 mg.

IT **171714-84-4**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)(multicomponent pharmaceutical formulations for treatment of cardiovascular disorders)

RN 171714-84-4 CAPLUS

CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

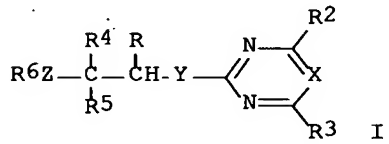
Absolute stereochemistry.



L11 ANSWER 126 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1999:234122 CAPLUS Full-text
DN 130:257363
TI Multicomponent pharmaceutical formulations for treatment of cardiovascular disorders
IN Muenter, Klaus; Kirchengast, Michael; Korioth, Horst
PA Knoll A.-G. Chemische Fabriken, Germany
SO Ger. Offen., 36 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 19742717	A1	19990401	DE 1997-19742717	19970926
	CA 2304712	AA	19990408	CA 1998-2304712	19980910
	WO 9916445	A1	19990408	WO 1998-EP5773	19980910
	W: AL, AU, BG, BR, BY, CA, CN, CZ, GE, HU, ID, IL, JP, KR, KZ, LT, LV, MK, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, US, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	AU 9895395	A1	19990423	AU 1998-95395	19980910
	AU 750755	B2	20020725		
	EP 1014989	A1	20000705	EP 1998-948954	19980910
	EP 1014989	B1	20040114		
	R: AT, BE, CH, DE, ES, FR, GB, IT, LI, NL, SE, FI				
	JP 2001517704	T2	20011009	JP 2000-513581	19980910
	AT 257706	E	20040115	AT 1998-948954	19980910
	RU 2222328	C2	20040127	RU 2000-110630	19980910
	ES 2214734	T3	20040916	ES 1998-948954	19980910
	US 6329384	B1	20011211	US 2000-508993	20000320
	NO 2000001548	A	20000324	NO 2000-1548	20000324
PRAI	DE 1997-19742717	A	19970926		
	DE 1997-19743141	A	19970930		
	WO 1998-EP5773	W	19980910		

OS MARPAT 130:257363
GI



I

AB Novel combinations of an endothelin antagonist and an inhibitor of the renin-angiotensin system are provided for treatment of cardiovascular disorders. The endothelin antagonist is a pyrimidine- or triazine-substituted carboxylic acid [I; R = CHO, CN, CO2H, tetrazolyl, etc.; R2, R3 = H, OH, amino, halo, C1-4 alkyl, haloalkyl, alkoxy, etc.; R4, R5 = (substituted) Ph or naphthyl, C3-7 cycloalkyl; R6 = H, (substituted) alkyl, alkenyl, alkynyl, or cycloalkyl; X = N, CR14; R14 = H, C1-5 alkyl; or R14CCR3 = 5- or 6-membered ring; Y = O, S, single bond; Z = O, S, SO, SO2, single bond] or related compound Thus, administration of a combination of I (R = CO2H, R2 = R3 = OMe, R4 = R5 = Ph, R6 = Me, X = CH, Y = Z = O) (II) and trandolapril (2 and 10 mg/kg, resp.) orally to normal male beagles decreased their mean arterial pressure after 2 h by 30.9 mm Hg and increased the heart rate by 25.4/min. Hard gelatin capsules were prepared containing II 250.0, ramipril 2.5, lactose 18.0, PVP 15.0, microcryst. cellulose 17.5, Na carboxymethylstarch 10.0, talc 9.0, and Mg stearate 3.0 mg.

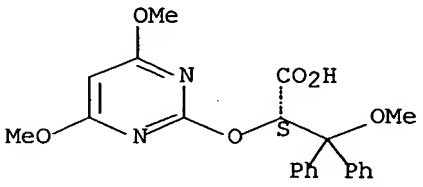
IT **171714-84-4**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(multicomponent pharmaceutical formulations for treatment of cardiovascular disorders)

RN 171714-84-4 CAPLUS

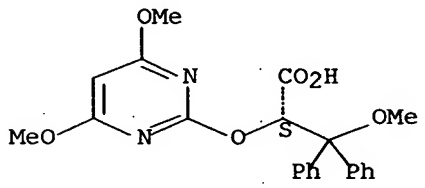
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L11 ANSWER 127 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1999:228856 CAPLUS Full-text
DN 131:39495
TI The ETA-receptor antagonist LU 135252 prevents the progression of established pulmonary hypertension induced by monocrotaline in rats
AU Dupuis, Jocelyn; Prie, Stephane
CS Department of Medicine, Institut de Cardiologie de Montreal, Montreal, QC, H1T 1C8, Can.
SO Journal of Cardiovascular Pharmacology and Therapeutics (1999), 4(1), 33-39
CODEN: JCPTFE; ISSN: 1074-2484
PB Churchill Livingstone
DT Journal
LA English
AB Background: An imbalance between the nitric oxide (NO) and endothelin systems may contribute to the development of pulmonary hypertension (PH). We evaluated the effect of the specific ETA-receptor antagonist LU 135252 (LU) in rats with established monocrotaline (MCT)-induced PH and the involvement of NO in the control of pulmonary vascular tone. Methods and Results: Two weeks after MCT, rats developed PH with a right ventricular pressure (RVP) of 42.3±8.5 vs 28.2±4.1 mmHg for controls (mean ± SD, P <.05). Daily oral therapy with LU (50 mg/kg) or saline was started 2 wk post-MCT injection for 20 days. LU increased the survival rate nonsignificantly from 41.7% to 66.7%. The surviving MCT + saline rats showed severe PH (RVP of 82.5±8.9 mmHg) and RV hypertrophy with a right-to-left ventricle + septum weight ratio of 69.6% ± 10.2%, which were improved by LU to 53.5±11.1 mmHg and 53.7% ± 9.9%, resp. (P <.01). In isolated lungs, pulmonary vascular compliance was reduced by PH and unaffected by LU therapy. After the NO synthase inhibitor Nω-nitro-L-arginine (10-4 mol/L), compliance was further reduced, although much less so, in the LU-treated group (P <.01). Conclusions: In this model, ETA antagonist therapy has a favorable effect on survival and pulmonary hemodynamics and reduces the dependency on NO for the attenuation of reduced vascular compliance.
IT **171714-84-4**, LU 135252
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ETA-receptor antagonist LU 135252 prevents progression of pulmonary hypertension induced by monocrotaline in rats)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

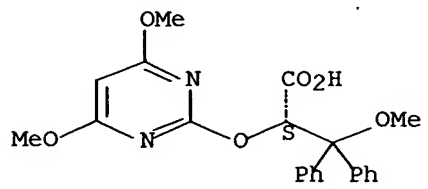
Absolute stereochemistry.



RE.CNT 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 128 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1998:803800 CAPLUS Full-text
DN 130:217899
TI Endothelin A receptor blockade causes adverse left ventricular remodeling but improves pulmonary artery pressure after infarction in the rat
AU Nguyen, Quang Trinh; Cernacek, Peter; Calderoni, Angelino; Stewart, Duncan J.; Picard, Pierre; Sirois, Pierre; White, Michel; Rouleau, Jean L.
CS Department of Medicine, Montreal Heart Institute, Montreal, QC, H1T 1C8, Can.
SO Circulation (1998), 98(21), 2323-2330
CODEN: CIRCAZ; ISSN: 0009-7322
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB Endothelin A (ETA) receptor antagonists have been shown to improve ventricular remodeling and survival in rats when started 10 days after infarction. Whether starting them earlier would have a more or less beneficial effect is uncertain. Rats surviving an acute myocardial infarction (MI) for 24 h (n=403) were assigned to saline or the ETA receptor antagonist LU 127043 or its active enantiomer LU 135252 for 4 wk. Chronic LU treatment had no effect on survival, with 46% of LU rats and 47% of saline-treated rats with large MI surviving to the end of the study. LU treatment led to scar thinning, further left ventricular (LV) dilatation, an increase in LV end-diastolic pressure, and an increase in wet lung weight ($P<0.05$). Despite this detrimental effect on LV function, LU led to a significant decrease in RV systolic (50±2 to 44±2 mm Hg, $P<0.05$ vs. saline) and right atrial pressures. LU treatment also prevented the increase in pulmonary ET-1 found in saline-treated rats with large MI but did not modify the increase in cardiac ET-1 in hearts with large MI. The early use of the ETA receptor antagonists LU 127043 or its active enantiomer LU 135252 after infarction in the rat leads to impaired scar healing and LV dilatation and dysfunction. This is accompanied by a decrease in RV systolic and right atrial pressures and a decrease in pulmonary but not cardiac ET-1 levels. It would thus appear that the early use of ETA receptor antagonists after infarction may be detrimental.
IT **171714-84-4**, LU 135252 **221176-51-8**, Lu 127043
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(endothelin A receptor blockade causes adverse left ventricular remodeling but improves pulmonary artery pressure after infarction in the rat)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

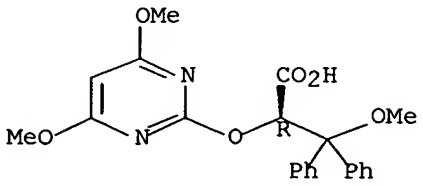
Absolute stereochemistry.



RN 221176-51-8 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-

methoxy-β-phenyl-, (αR)- (9CI) (CA INDEX NAME)

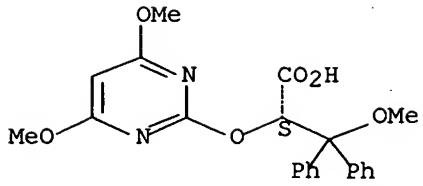
Absolute stereochemistry.



RE.CNT 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 129 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1998:765616 CAPLUS Full-text
DN 130:93791
TI Endothelin ETA receptor blockade restores NO-mediated endothelial function and inhibits atherosclerosis in apolipoprotein E-deficient mice
AU Barton, Matthias; Haudenschild, Christian C.; D'Uscio, Livius V.; Shaw, Sidney; Munter, Klaus; Luscher, Thomas F.
CS Cardiology, University Hospital Zurich and Cardiovascular Research Laboratory, Institute of Physiology, University of Zurich, Zurich, CH-8091, Switz.
SO Proceedings of the National Academy of Sciences of the United States of America (1998), 95(24), 14367-14372
CODEN: PNASA6; ISSN: 0027-8424
PB National Academy of Sciences
DT Journal
LA English
AB This study investigated whether endothelin-1 (ET-1), a potent vasoconstrictor, which also stimulates cell proliferation, contributes to endothelial dysfunction and atherosclerosis. Apolipoprotein E (apoE)-deficient mice and C57BL/6 control mice were treated with a Western-type diet to accelerate atherosclerosis with or without ETA receptor antagonist LU135252 (50 mg/kg/d) for 30 wk. Systolic blood pressure, plasma lipid profile, and plasma nitrate levels were determined In the aorta, NO-mediated endothelium-dependent relaxation, atheroma formation, ET receptor-binding capacity, and vascular ET-1 protein content were assessed. In apoE-deficient but not C57BL/6 mice, severe atherosclerosis developed within 30 wk. Aortic ET-1 protein content and binding capacity for ETA receptors was increased as compared with C57BL/6 mice. In contrast, NO-mediated, endothelium-dependent relaxation to acetylcholine (56 vs. 99%) and plasma nitrate were reduced (57.9 vs. 93 μM). Treatment with the ETA receptor antagonist LU135252 for 30 wk had no effect on the lipid profile or systolic blood pressure in apoE-deficient mice, but increased NO-mediated endothelium-dependent relaxation (from 56 to 93%, vs. untreated) as well as circulating nitrate levels (from 57.9 to 80 μM). Chronic ETA receptor blockade reduced elevated tissue ET-1 levels comparable with those found in C57BL/6 mice and inhibited atherosclerosis in the aorta by 31% without affecting plaque morphol. or ET receptor-binding capacity. Thus, chronic ETA receptor blockade normalizes NO-mediated endothelial dysfunction and reduces atheroma formation independent of plasma cholesterol and blood pressure in a mouse model of human atherosclerosis. ETA receptor blockade may have therapeutic potential in patients with atherosclerosis.
IT **171714-84-4**, LU135252
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(endothelin ETA receptor blockade restores NO-mediated endothelial function and inhibits atherosclerosis in apolipoprotein E-deficient mice)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 130 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1998:635651 CAPLUS Full-text
DN 129:275935
TI Novel pyrimidine- and triazine-containing carboxylic acid derivatives, their preparation, and use as endothelin receptor antagonists in treating cancer
IN Romerdahl, Cynthia A.
PA BASF A.-G., Germany
SO PCT Int. Appl., 100 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9841206	A1	19980924	WO 1998-US4596	19980309
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	US 6030975	A	20000229	US 1997-818622	19970314
	CA 2283732	AA	19980924	CA 1998-2283732	19980309
	AU 9866946	A1	19981012	AU 1998-66946	19980309
	AU 744019	B2	20020214		
	EP 969841	A1	20000112	EP 1998-909067	19980309
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, FI, RO				
	BR 9808263	A	20000516	BR 1998-8263	19980309
	JP 2001517220	T2	20011002	JP 1998-540573	19980309
	ZA 9802136	A	19990913	ZA 1998-2136	19980313
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	WO 1998-US4596	W	19980309		

OS MARPAT 129:275935
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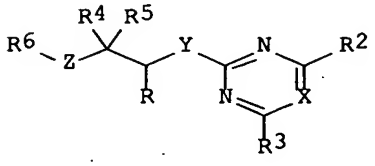

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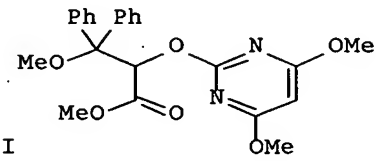


II

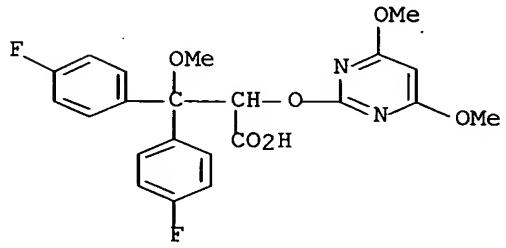
AB The invention provides a method for treating cancer, wherein the cancer is a tumor in which endothelin (ET) is upregulated (e.g. tumors of the prostate, lung, liver, breast, brain, stomach, colon, endometrium, testicle, thyroid, pituitary, bladder, kidney, pancreas and meninges), by administering a compound I [R = CHO, tetrazolyl, cyano, CO2H or its hydrolyzable derivs.; R2 = H, OH, (di)(alkyl)amino, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, alkylthio; X = N, CH, C-alkyl, or forms a 5- or 6-ring to R3; R3 = groups

given for R2, or NHO-alkyl, or forms 5- or 6-ring to X; R4, R5 = (un)substituted Ph, naphthyl, or certain fused derivs.; or R4 = a wide variety of possible substituents and R5 = H, alk(en/yn)yl, cycloalkyl, haloalkyl, Ph, etc.; or R4R5 forms (un)substituted 3- to 8-ring; R6 = H, (un)substituted alk(en/yn)yl, cycloalkyl, Ph, naphthyl, heteroaryl; Y, Z = S, O, bond; with provisos]. Over 150 compds. were prepared For instance, methanolysis of Me 3,3-diphenyl-2,3-epoxypropionate in the presence of BF3.OEt2 gave 88% Me 2-hydroxy-3-methoxy-3,3-diphenylpropionate, which was etherified with 4,6-dimethoxy-2-(methylsulfonyl)pyrimidine to give 82% title compound II. At 150 mg/kg/day i.p. in mice in the DU-145 prostate tumor model, II reduced mean tumor weight to 33% of control after 10 days.

IT **177036-81-6P 177036-86-1P 177036-87-2P**
178306-45-1P 178306-46-2P 178306-57-5P
178306-66-6P 178306-67-7P 178306-69-9P
178306-83-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of pyrimidine- and triazine-containing carboxylic acid derivs. as
endothelin-based anticancer agents)

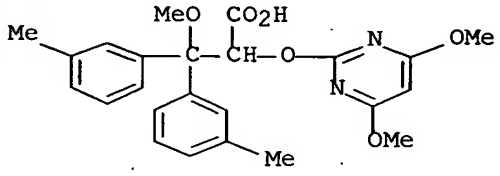
RN 177036-81-6 CAPLUS

CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-4-fluoro-β-(4-fluorophenyl)-β-methoxy- (9CI) (CA INDEX NAME)



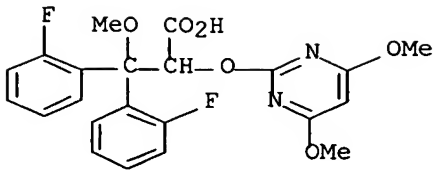
RN 177036-86-1 CAPLUS

CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-3-methyl-β-(3-methylphenyl)- (9CI) (CA INDEX NAME)



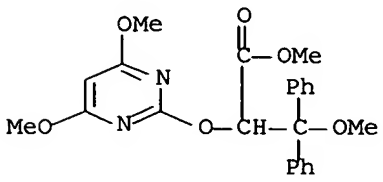
RN 177036-87-2 CAPLUS

CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-2-fluoro-β-(2-fluorophenyl)-β-methoxy- (9CI) (CA INDEX NAME)



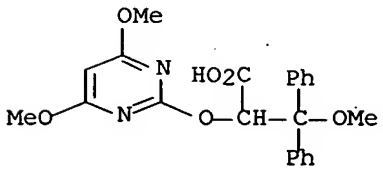
RN 178306-45-1 CAPLUS

CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, methyl ester (9CI) (CA INDEX NAME)



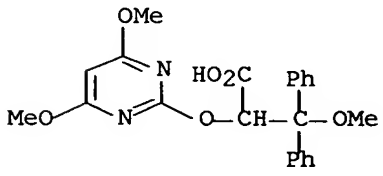
RN 178306-46-2 CAPLUS

CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl- (9CI) (CA INDEX NAME)



RN 178306-57-5 CAPLUS

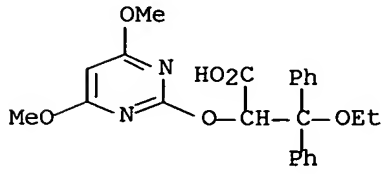
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, sodium salt (9CI) (CA INDEX NAME)



● Na

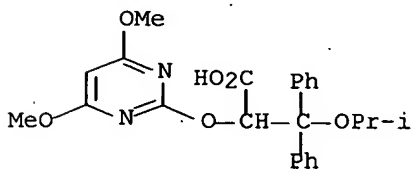
RN 178306-66-6 CAPLUS

CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-ethoxy-β-phenyl- (9CI) (CA INDEX NAME)



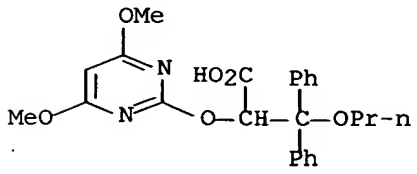
RN 178306-67-7 CAPLUS

CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-(1-methylethoxy)-β-phenyl- (9CI) (CA INDEX NAME)



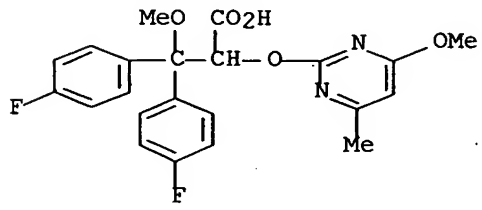
RN 178306-69-9 CAPLUS

CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-phenyl-β-propoxy- (9CI) (CA INDEX NAME)



RN 178306-83-7 CAPLUS

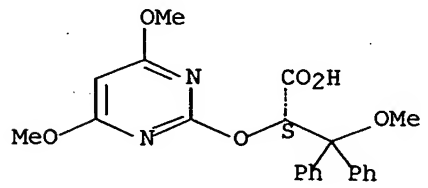
CN Benzenepropanoic acid, 4-fluoro-β-(4-fluorophenyl)-β-methoxy-α-[(4-methoxy-6-methyl-2-pyrimidinyl)oxy]- (9CI) (CA INDEX NAME)



RE.CNT 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 131 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1998:628694 CAPLUS Full-text
DN 129:325919
TI The endothelin A receptor antagonist LU 135252 protects the myocardium from neutrophil injury during ischemia/reperfusion
AU Gonon, Adrian T.; Wang, Qing-Dong; Pernow, John
CS Department of Cardiology, Karolinska Hospital, Stockholm, 171 76, Swed.
SO Cardiovascular Research (1998), 39(3), 674-682
CODEN: CVREAU; ISSN: 0008-6363
PB Elsevier Science B.V.
DT Journal
LA English
AB Endothelin-1 (ET-1) is not only a potent vasoconstrictor but also a stimulator of polymorphonuclear leukocyte (PMN) aggregation and adhesion. The aim of this study was to investigate whether an ETA receptor antagonist attenuates the PMN-mediated contractile dysfunction following myocardial ischemia. Isolated rat hearts were perfused according to the Langendorff method. The hearts were subjected to global ischemia and reperfused with buffer solution only, or human PMNs dissolved in rat plasma (HNRP). In an initial study, the ETA receptor antagonist LU 135252 (1 and 10 μmol/L) or ET-1 (1 and 10 nmol/L) did not significantly affect the recovery of left ventricular developed pressure (LVDP), end-diastolic pressure (LVEDP), the first derivative of left ventricular pressure (dP/dt) or the rate pressure product (RPP) during reperfusion with buffer solution only compared to a vehicle group. In a second study on hearts reperfused with HNRP, administration of LU 135252 (10 μmol/L) significantly enhanced the recovery of LVDP, dP/dt and RPP in hearts reperfused with HNRP. LVEDP was 20 mmHg lower in hearts given LU 135252 than vehicle in combination with HNRP ($P<0.05$). Outflow of PMNs in the coronary effluent during reperfusion was 41±8% in hearts given LU 135252 compared to 9±5% in vehicle-treated hearts ($P<0.01$). There was a significant correlation between the myocardial functional recovery and the outflow of PMNs. Administration of ET-1 (0.1 and 1 nmol/L) in combination with HNRP resulted in complete loss of contractile function and no outflow of PMNs during reperfusion. The ETA receptor antagonist LU 135252 protects from ischemia/reperfusion injury in the isolated rat heart in the presence of PMNs. It is suggested that inhibition of PMN-induced injury during reperfusion is an important cardioprotective action of LU 135252.
IT **171714-84-4**, LU 135252
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(endothelin A receptor antagonist LU 135252 protects myocardium from neutrophil injury during ischemia/reperfusion)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

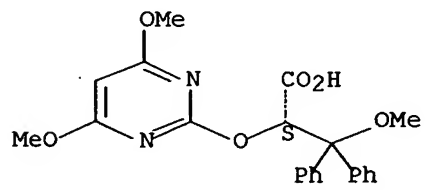
Absolute stereochemistry.



RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 132 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1998:628675 CAPLUS Full-text
DN 129:329204
TI Chronic blockade of endothelin ETA receptors improves flow dependent dilation in resistance arteries of hypertensive rats
AU Iglarz, Marc; Matrougui, Khalid; Levy, Bernard I.; Henrion, Daniel
CS Institut National de la Sante et de la Recherche Medicale, Universite Paris, Paris, 75475, Fr.
SO Cardiovascular Research (1998), 39(3), 657-664
CODEN: CVREAU; ISSN: 0008-6363
PB Elsevier Science B.V.
DT Journal
LA English
AB Flow (shear stress)-induced dilation (FD) is attenuated in hypertension. Flow triggers the release by endothelial cells of dilators, such as NO or cyclo-oxygenase (COX) derivs. and constrictor factors such as endothelin-1 (ET-1) which might be involved in several cardiovascular diseases. The authors hypothesized that ET-1 might play a functional role in FD and participate in the endothelial dysfunction in hypertension. The authors investigated the effect of a chronic treatment with the ETA receptor blocker LU135252 (50 mg/kg/day) for 2 wk on the dilator response to flow in normotensive (Wistar-Kyoto; WKY) or hypertensive (SHR, or 8 per group) rats. Systolic arterial pressure was not significantly affected by chronic ETA receptor blockade in both strains. In mesenteric resistance arteries (diameter: approx. 100 μm), isolated in vitro, FD was lower and myogenic tone higher in SHR than in WKY rats. Chronic ETA receptor blockade increased FD by 73% (7.5 to 13.0 μm dilation with a flow-rate of 150 μl/min) in SHR (no effect in WKY). The participation of NO to FD was increased in SHR and the participation of dilator COX product(s) (blocked by indomethacin 10 μmol/l) to FD was significantly increased in SHR and in WKY. In control rats FD was improved by acute ETA receptor blockade in WKY rats (18.5 to 23.2 μm dilation to flow-rate of 150 μl/min) and significantly more in SHR (6.0+ 1.8 to 15.11.6 am). Acetylcholine-induced dilation was also improved by chronic ETA receptor blockade (no effect of an acute blockade). Myogenic and phenylephrine-induced tone were not affected by chronic or acute ETA receptor blockade. The improvement of endothelium-dependent dilation was not related to a change in blood pressure. Thus, chronic ETA receptor blockade increased flow-induced dilation in SHR possibly by suppressing flow-induced ETA stimulation and by improving the release of dilator products by the endothelium.
IT **171714-84-4**, LU135252
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(chronic blockade of endothelin ETA receptors with LU135252 improves flow dependent dilation in resistance arteries of hypertensive rats in relation to role or endothelin-1)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

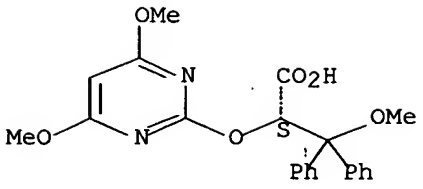
Absolute stereochemistry.



RE.CNT 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD

L11 ANSWER 133 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1998:628434 CAPLUS Full-text
DN 129:325917
TI Selective ETA receptor blockade prevents left ventricular remodeling and deterioration of cardiac function in experimental heart failure
AU Mulder, Paul; Richard, Vincent; Bouchart, Frangois; Derumeaux, Genevieve; Munter, Klaus; Thuillez, Christian
CS Department of Pharmacology, Rouen University Medical School, Christian, Fr.
SO Cardiovascular Research (1998), 39(3), 600-608
CODEN: CVREAU; ISSN: 0008-6363
PB Elsevier Science B.V.
DT Journal
LA English
AB Left ventricular (LV) dilation, which is a predictor of survival in humans with chronic heart failure (CHF), is limited by a mixed endothelin ETA-ETB antagonist. Whether selective ETA receptor blockade influences LV dilation is unknown. The authors determined, in a rat model of CHF, the effects of the ETA receptor blocker LU 135 252 on LV remodeling. Rats were subjected to coronary artery ligation and treated for ten weeks with placebo or LU 135 252 (LU), at a dose of 10 or 30 mg kg-1 day-1. Systolic blood pressure and heart rate (plethysmog.) were determined in conscious animals before and after four and ten weeks of treatment. At these time points, cardiac output and LV dimensions were measured in anesthetized rats by transthoracic echocardiog. LV hemodynamics were determined in anesthetized rats after ten weeks. Pressor responses to ET-1 (1 nmol/kg, i.v.) and sarafotoxin S6c (0.3 ng/kg, i.v.) were measured, to assess the efficacy of ET receptor antagonism and the lack of blockade of ETB receptor blockade, resp. The pressor response to ET-1 was significantly reduced by LU (% change in systolic blood pressure: sham: 9±1; CHF: 5±1; CHF LU: 0±3 and -4±2% for the low and high dose, resp.). LU did not affect the response to sarafotoxin (CHF: -37±3; CHF LU: -29±3 and -28±2% for the low and high dose, resp.). Both doses of LU decreased systolic blood pressure, but only the high dose of LU reduced heart rate. Furthermore, LU restored cardiac output dose-dependently throughout the study. Both doses of LU limited LV dilatation and deterioration of LV fractional shortening to the same extent. After ten weeks, LU normalized LV end-diastolic- and central venous pressures, but did not affect LV dP/dtmax or dP/dtmin. LU did not prevent the development of cardiac hypertrophy, but reduced LV collagen d. In this rat model, the selective ETA receptor blocker LU, at the dose of 30 mg kg-1 day-1, reduced blood pressure and heart rate, limited progressive left ventricular remodeling and improved cardiac hemodynamics and function. These effects of LU might have important clin. relevance in the treatment of heart failure.
IT **171714-84-4**, LU 135252
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(selective ETA receptor blockade prevents left ventricular remodeling and deterioration of cardiac function in exptl. heart failure)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

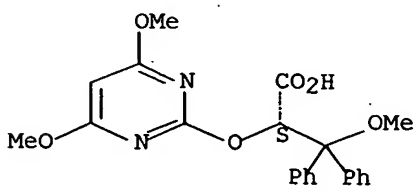
Absolute stereochemistry.



RE.CNT 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 134 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1998:628323 CAPLUS Full-text
DN 129:325915
TI Beneficial effects of long-term selective endothelin type A receptor blockade in canine experimental heart failure
AU Moe, Gordon W.; Albernaz, Ana; Naik, George O.; Kirchengast, Michael; Stewart, Uncan J.
CS Terrence Donnelly Heart Centre, University of Toronto, Toronto, ON, MSB 1W8, Can.
SO Cardiovascular Research (1998), 39(3), 571-579
CODEN: CVREAU; ISSN: 0008-6363
PB Elsevier Science B.V.
DT Journal
LA English
AB The objective was to examine the effects of chronic type A endothelin receptor (ETA) blockade in a dog model of pacing-induced cardiomyopathy. Eight dogs received an ETA antagonist, LU 135252 (50 mg/kg orally daily) and nine dogs received a matching placebo starting at day three of pacing and continued for the remainder of the three weeks of pacing. In the placebo group, the mean pulmonary artery pressure and left ventricular end diastolic pressure increased from 163±3 and 8±2 mmHg, resp., at baseline to 40±11 and 34±7 mmHg, resp., at two weeks (both $p<0.001$ vs. baseline). Cardiac output declined from 3.5±0.7 to 1.9±0.6 1/min ($p<0.001$). In the treatment group, LU 135252 attenuated the increase in mean pulmonary artery and left ventricular end diastolic pressure (16±3 and 9±1 mmHg at baseline to 29±3 and 27±3 mmHg, resp., at two weeks, $p<0.001$), and the decline in cardiac output (3.2±0.3 to 2.6±0.8 1/min, $p<0.01$; $p<0.05$ vs. placebo for the three parameters). Systemic and pulmonary vascular resistance increased only in the placebo group. Left ventricular end-diastolic volume increased to a similar degree. However, LU 135252 attenuated the increase in plasma norepinephrine level (placebo, 1.2±0.5 to 3.7±1.9 pmol/l; treatment, 0.8±0.3 to 2.4±0.6 pmol/l; both $p<0.001$ vs. baseline; $p<0.05$ vs. placebo). Our results suggest that endothelin-1 plays a role in the hemodynamic perturbations in canine pacing-induced cardiomyopathy. The favorable hemodynamic effects without concomitant aggravation of neurohormonal activation suggests that ETA receptor blockade may be beneficial in the treatment of heart failure.
IT **171714-84-4**, LU 135252
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(beneficial effects of long-term selective endothelin type A receptor blockade by LU 135252 in canine exptl. heart failure)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

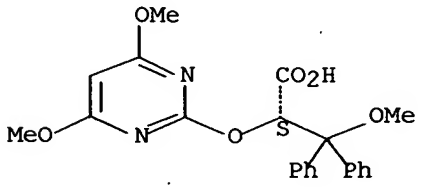
Absolute stereochemistry.



RE.CNT 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 135 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1998:533678 CAPLUS Full-text
DN 129:170060
TI Radioreceptor assay of an endothelin A receptor antagonist in plasma and urine
AU Cernacek, Peter; Franchi, Luigi; Dupuis, Jocelyn; Rouleau, Jean-Lucien; Levy, Mortimer
CS Department of Laboratory Medicine, Montreal Heart Institute, Montreal, QC, H1T 1C8, Can.
SO Clinical Chemistry (Washington, D. C.) (1998), 44(8, Pt. 1), 1666-1673
CODEN: CLCHAU; ISSN: 0009-9147
PB American Association for Clinical Chemistry
DT Journal
LA English
AB Orally active nonpeptide antagonists of endothelin (ET) receptors may prove beneficial in the treatment of cardiovascular and renal disease. The pharmacodynamics and pharmacokinetics of these drugs are not sufficiently known, and practical methods for their anal. were not developed. A simple, sensitive, and reproducible radioreceptor assay (RRA) is described for LU135252, a selective antagonist of the ETA receptor, using porcine aortic smooth muscle membranes as the acceptor and 125I-endothelin-1 as the ligand. With MeOH extraction of blood plasma and urine samples, recovery of LU135252 ranged from 79-91% at 60-1000 nmol/L. The logit-log transformed calibration curves constructed with LU135252 added to plasma or to urine were linear (n=11) in the range from 18.7-2400 nmol/L. The detection limit with plasma- and urine-based calibration curves was 19 nmol/L. The interassay coefficient of variation was 12.6% at 70 nmol/L (n=9) and 6.5% at 590 nmol/L (n=9). Endothelin-1 did not interfere in the RRA at pathophysiol. and clin. relevant concns. [≤15 pmol/L (40 pg/mL)]. When LU135252 was added to plasma, the signal was completely stable after storage for 1 wk at 4°, although there was a modest loss of the signal after 24 h at room temperature The practical performance of this RRA was then tested in plasma samples obtained from (a) rats after a single oral administration of LU135252, (b) from coronary-ligated rats chronically treated with LU135252, and (c) in plasma and urine samples obtained from dogs during intrarenal infusion of LU135252.
IT **171714-84-4**, LU135252
RL: ANT (Analyte); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)
(radioreceptor assay of LU135252 in plasma and urine)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

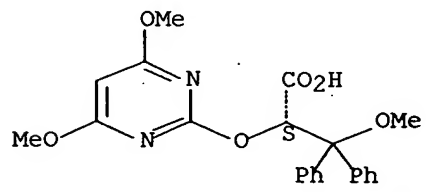
Absolute stereochemistry.



RE.CNT 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 136 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1998:521451 CAPLUS Full-text
DN 129:285775
TI Renoprotective effect of simultaneously blocking of angiotensin II and endothelin-1 in rats with membranous nephropathy
AU Benigni, Ariela; Corna, Daniela; Maffi, Raffaello; Benedetti, Giuditta; Zoja, Carla; Remuzzi, Giuseppe
CS Mario Negri Institute for Pharmacological Research, and Division of, Bergamo, Italy
SO Kidney International (1998), 54(2), 353-359
CODEN: KDYIA5; ISSN: 0085-2538
PB Blackwell Science, Inc.
DT Journal
LA English
AB We previously showed that chronic administration of an angiotensin converting enzyme (ACE) inhibitor to rats with passive Heymann nephritis (PHN), a model of membranous nephropathy with proteinuria and increased renal synthesis of endothelin-1 (ET-1), reduces urinary proteins and partially limits the exaggerated ET-1 renal synthesis. Here we compared the effect of an ETA receptor antagonist and an ACE-inhibitor given as single therapies with a combination of the two drugs in uninephrectomized PHN rats. PHN was induced with a single i.v. injection of rabbit anti-Fx1A antibody in 40 male Sprague Dawley rats. To accelerate the onset of renal damage rats underwent uninephrectomy seven days later and were subsequently treated until eight months with the ETA receptor antagonist LU-135252 (50 mg/kg b.i.d. p.o.) or the ACE-inhibitor trandolapril (1 mg/kg in the drinking water) or the combination of the two drugs. Either LU-135252 or trandolapril given alone prevented the increase in systolic blood pressure (SBP). Combined therapy was even more effective than single drugs. While LU-135252 and trandolapril reduced proteinuria by 23 to 25%, the drug combination resulted in 45% lowering of urinary proteins. Serum creatinine was significantly decreased by the combination, but not by the single drugs. Glomerulosclerosis and tubulointerstitial damage were more reduced by combined therapy than by LU-135252 or trandolapril alone. These data suggest that simultaneously blocking angiotensin II (Ang II) and ET-1 in an accelerated model of PHN had an additive renoprotective effect than single blocking Ang II or ET-1 and would represent a therapeutic advantage for renal disease patients who do not completely respond to ACE inhibitors.
IT **171714-84-4**, LU-135252
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(renoprotective effect of simultaneously blocking of angiotensin II and endothelin-1 in membranous nephropathy)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

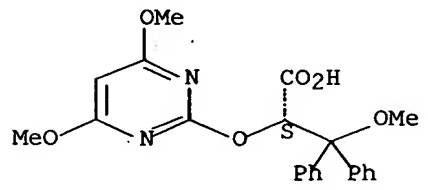
Absolute stereochemistry.



RE.CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 137 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1998:429152 CAPLUS Full-text
DN 129:170303
TI Improvement of postischemic acute renal failure with the novel orally active endothelin-A receptor antagonist LU 135252 in the rat
AU Birck, Rainer; Knoll, Thomas; Braun, Claude; Kirchengast, Michael; Munter, Klaus; Van Der Woude, Fokko J.; Rohmeiss, Peter
CS V. Dep. Med. Klinikum Mannheim, Univ. Heidelberg, Mannheim, Germany
SO Journal of Cardiovascular Pharmacology (1998), 32(1), 80-86
CODEN: JCPCDT; ISSN: 0160-2446
PB Lippincott-Raven Publishers
DT Journal
LA English
AB The endothelin (ET) system may play an important role in the pathogenesis of acute renal failure (ARF). We hypothesize that the course of ARF in an ischemia-reperfusion model will be markedly attenuated by the orally active ETA-receptor antagonist LU 135252 (LU) because of an improvement of renal perfusion. ARF was induced in rats by clamping both renal arteries for 60 min. The study was divided into two parts. In part 1, Rats received LU orally (100 mg/kg/day) starting 1 h after induction of ARF for 14 days. Crs, Clcr and FEna were measured on days 1, 6, 9, and 14 after ARF. Crs was lower in the treatment group on days 1 [1.3±0.31 mg/dL (n = 9) vs. 2.7±0.46 mg/dL (n = 10); $p < 0.05$] and 6[0.5±0.1 mg/dL (n = 9) vs. 1.0±0.2 mg/dL (n = 9); $p < 0.05$], and Clcr was higher on day 1[0.9±0.17 mL/min (n = 9) vs. 0.2±0.1 mL/min (n = 8); $p < 0.05$] and 6[1.8±0.29 mL/min (n = 9) vs. 1.0±0.21 mL/min (n = 9); $p < 0.05$] compared with vehicle. Addnl., FEna was lower in treated rats on day 1 [1±0.4% (n = 9) vs. 8±3% (n = 8); $p < 0.05$] compared with vehicle. In part 2, ARF was induced as described. Treated animals received 10 mg/kg LU on days 0, 1, 3, 6, 9, and 14 after ARF as an i.v. bolus injection. RBF, cortex blood flow (CBF), and medulla blood flow (MBF) were measured after application of LU on the same days: LU induced as increase in RBF (day 1: 14±5.3%, n = 6, p = 0.04; day 3: 15±2.8%, n = 8; p = 0.0008; day 6: 21±5.8%, n = 6, p = 0.0.02; day 9: 13±4%, n = 6; p = 0.03) and CBF (day 1: 8±2.2%, n = 7, p = 0.03; day 3: 7±2.5%, n = 7; p = 0.05; day 6: 18± 4.8%, n = 6, p = 0.04; day 9: 10±2.5%, n = 6; p = 0.008) up to the first 9 days. MBF did increase on days 1 (9±3.1%, n = 6; p = 0.04) and 6 (13±3.6%, n = 6; p = 0.03). Our data confirm the hypothesis that ET plays a major role in the genesis of ARF associated with ischemia-reperfusion.
IT **171714-84-4**, LU 135252
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(improvement of postischemic acute renal failure with the novel orally active endothelin-A receptor antagonist LU 135252 in the rat)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

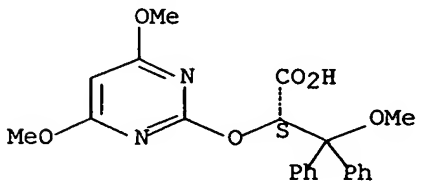
Absolute stereochemistry.



RE.CNT 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 138 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1998:387140 CAPLUS Full-text
DN 129:144742
TI EndothelinA receptor blockade improves nitric oxide-mediated vasodilation in monocrotaline-induced pulmonary hypertension
AU Prie, Stephane; Stewart, Duncan J.; Dupuis, Jocelyn
CS Deps. Med., Montreal Heart Inst., Montreal, QC, Can.
SO Circulation (1998), 97(21), 2169-2174
CODEN: CIRCAZ; ISSN: 0009-7322
PB Williams & Wilkins
DT Journal
LA English
AB Nitric oxide (NO) and endothelin (ET) have been implicated in the pathogenesis of pulmonary hypertension (PH). Chronic ETA antagonist therapy reduces PH in monocrotaline (MCT)-treated rats. Interactions between the L-arginine-NO pathway and the ET system have been described. We therefore studied the effect of long-term treatment with an oral ETA antagonist (LU 135252) on NO-related vasodilation in isolated lungs from control rats and rats with MCT-induced PH. Three weeks after MCT injection, PH was associated with an increase in right ventricular pressure (from 27.4±0.0 to 66.6±4.1 mm Hg) and a decrease in endothelium-independent vasodilation in response to sodium nitroprusside (10-10 to 10-5 mol/L; ΔEmax, from 11.1±0.9 to 2.7±0.3 mm Hg). Endothelium-dependent vasodilation in response to acetylcholine (10-9 to 10-4 mol/L) and the calcium ionophore A23187 (10-9 to 10-7 mol/L) remained unaffected. Treatment with LU 135252 did not significantly affect the endothelium-dependent and -independent vasodilations in control rats. However, in MCT-treated rats, LU 135252 therapy significantly reduced right ventricular pressure (39.7±2.1 mm Hg), potentiated acetylcholine-induced vasodilation (ΔEmax, from 1.6±0.2 to 3.7±0.4 mm Hg), and improved the responses to sodium nitroprusside (ΔEmax, from 2.7±0.3 to 5.6±0.6 mm Hg). LU 135252 did not significantly alter the non-receptor-mediated endothelium-dependent vasodilation to A23187 or pulmonary constitutive NO synthase activity. MCT PH is associated with a reduced smooth muscle responsiveness to NO but a maintained endothelium-dependent vasodilatory potency. Long-term ETA antagonist therapy not only restores smooth muscle responsiveness to NO but also increases endothelium-dependent dilation in response to acetylcholine. This mechanism may contribute to the therapeutic benefit of ETA antagonists in PH.
IT **171714-84-4**, LU 135252
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pulmonary hypertension treatment by ETA antagonists)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

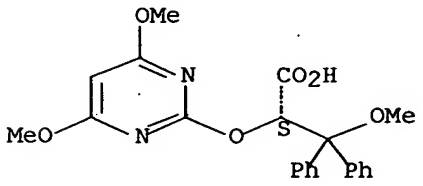
Absolute stereochemistry.



RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 139 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1998:383357 CAPLUS Full-text
DN 129:131067
TI The novel non-peptide selective endothelin A receptor antagonist LU 135 252 protects against myocardial ischemic and reperfusion injury in the pig
AU Gonon, A. T.; Wang, Q. -D.; Shimizu, M.; Pernow, J.
CS Department of Cardiology, Karolinska Hospital, Stockholm, S-171 76, Swed.
SO Acta Physiologica Scandinavica (1998), 163(2), 131-137
CODEN: APSCAX; ISSN: 0001-6772
PB Blackwell Science Ltd.
DT Journal
LA English
AB The aim of the study was to investigate the efficacy of the novel non-peptide selective endothelin A (ETA) receptor antagonist LU 135 252 to limit the extent of myocardial ischemic and reperfusion injury. Administration of LU 135 252 (1 and 5 mg kg-1 i.v.) to anesthetized pigs reduced mean arterial pressure (MAP) from 91 ± 4 to 79 ± 3 mmHg ($P < 0.05$) and 96 ± 3-82 ± 3 mmHg ($P < 0.01$), resp. Heart rate, coronary blood flow and coronary vascular resistance were not affected by LU 135 252. The infarct size induced by 45-min ligation of the left anterior descending coronary artery (LAD) followed by 4-h reperfusion in pigs was 81 ± 5% of the area at risk in control animals given vehicle (n = 8). In pigs receiving 1 mg kg-1 (n = 6) or 5 mg kg-1 (n = 8) of LU 135 252 i.v. 20 min before ischemia the infarct size was reduced to 64 ± 3% ($P < 0.05$) and 35 ± 4% ($P < 0.001$), resp., of the area at risk. During the reperfusion period there was a non-significant trend towards a higher coronary blood flow and a lower coronary vascular resistance in the groups given LU 135 252 compared to controls. Myocardial overflow of ET-like immunoreactivity was increased during the reperfusion period but it was not affected by administration of LU 135 252. It is concluded that administration of the selective ETA receptor antagonist LU 135 252 effectively protects the myocardium from ischemia/reperfusion injury, indicating that the ETA receptor subtype is involved in the development of ischemia/reperfusion injury.
IT **171714-84-4**, LU 135252
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(endothelin A receptor antagonist LU 135 252 protects against myocardial ischemic and reperfusion injury)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

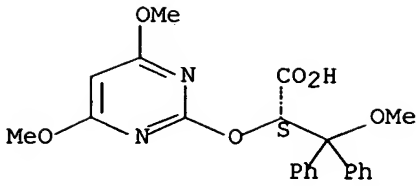
Absolute stereochemistry.



RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 140 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1998:383001 CAPLUS Full-text
DN 129:157044
TI Effect of chronic treatment with two different ETA selective endothelin receptor antagonists on blood pressure and small artery structure of deoxycorticosterone acetate (DOCA)-salt hypertensive rats
AU Li, Jin-S.; Turgeon, Andre; Schiffrin, Ernesto L.
CS MRC Multidisciplinary Research Group on Hypertension, Clinical Research Institute of Montreal, University of Montreal, Montreal, QC, H2W 1R7, Can.
SO American Journal of Hypertension (1998), 11(5), 554-562
CODEN: AJHYE6; ISSN: 0895-7061
PB Elsevier Science Inc.
DT Journal
LA English
AB Chronic treatment with a combined ETA and ETB endothelin receptor antagonist blunts hypertension development and small artery hypertrophy in deoxycorticosterone acetate (DOCA)-salt treated rats, in which endothelin-1 is overexpressed in endothelial cells of blood vessels. To determine whether ETA receptor antagonism played a predominant role in these findings, in this study the effects of two orally active ETA selective endothelin receptor antagonists, A-127722.5 and LU 135252, were evaluated on blood pressure and small artery structure in DOCA-salt hypertensive rats. Rats received A-127722.5 (30 mg/kg/day) or LU 135252 (50 mg/kg/day) in their drinking water since induction of hypertension. Whereas three of 10 untreated DOCA-salt hypertensive rats died, in the two treated groups none died and all appeared healthier. Systolic blood pressure of treated DOCA-salt hypertensive rats, measured with the tail cuff method, was lower than that of untreated DOCA-salt hypertensive rats by a mean of 20 mm Hg after 4 wk of treatment with A-127722.5 and by 14 mm Hg with LU 135252. Cardiac and aortic relative wts. were unaffected by treatment with either agent. Small arteries of the mesenteric, coronary, renal, and femoral vasculature, examined under standardized conditions after mounting on a wire myog., were found to exhibit significant inward hypertrophic remodeling in DOCA-salt hypertensive rats. DOCA-salt hypertensive rats treated with A-127722.5 had a significantly smaller media width and media-to-lumen ratio in the four vascular beds examined, and rats treated with LU 135252 showed these findings in mesenteric and renal small arteries. These results demonstrate that chronic ETA selective antagonism induces similar effects to those of combined ETA/ETB receptor antagonists in DOCA-salt hypertensive rats; namely, mild reduction in development of hypertension and blunting of small artery morphol. changes, and also appears to improve survival. These results suggest a role of ETA receptors in the endothelin dependent component of blood pressure elevation in DOCA-salt hypertensive rats, and in the small artery morphol. changes present in this model of exptl. hypertension.
IT **171714-84-4**, LU 135252
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ETA selective endothelin receptor antagonists effect on blood pressure and small artery structure of deoxycorticosterone acetate-salt hypertensive rats)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

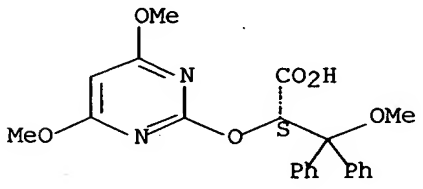
Absolute stereochemistry.



RE.CNT 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 141 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1998:312818 CAPLUS Full-text
DN 129:49426
TI Endothelin-A receptor antagonist combined with hydralazine improves survival and renal function in hypertensive rats
AU Munter, K.; Hergenroder, S.; Kirchengast, M.
CS Cardiovascular Pharmacology, Knoll AG, Ludwigshafen, 67008, Germany
SO Journal of Cardiovascular Pharmacology (1998), 31(Suppl. 1, Endothelin V), S245-S248
CODEN: JCPCDT; ISSN: 0160-2446
PB Lippincott-Raven Publishers
DT Journal
LA English
AB To investigate the role of endothelin (ET) in severe hypertension, endothelial dysfunction hypercholesterolemic stroke-prone spontaneously hypertensive rats (SHRSP on a 5% cholesterol diet) were addnl. fed with 1% NaCl and 0.023% nitro-L-arginine. Under these conditions, all untreated rats died within 30 days (median 17 days). A significant prolongation of survival (median 33 days) was achieved by combination treatment with hydralazine and the ETA receptor antagonist LU 135252. Monotherapy was less effective (LU 135252 18 days; hydralazine 28 days). Likewise, only treatment with the combination completely prevented the increase in systolic arterial pressure (SAP) seen in the control group during the first 10 days and delayed development of hypertension during the subsequent observation period. The superior efficacy of the combination was also reflected by improved kidney function. After 20 days of treatment, proteinuria had only increased to 1,272 ± 135 mg/kg/day, a reduction of 45% compared to the untreated control group (2,300 ± 346 mg/kg/day; $p < 0.05$). In this animal model of aggravated hypertension and endothelial dysfunction, the combination of LU 135252 with hydralazine was superior compared to either monotherapy. Therefore, the combination of an ETA receptor antagonist with vasodilators may be a potent therapy to improve blood pressure, renal function, and survival in severe hypertension with concomitant metabolic disease.
IT **171714-84-4**, LU 135252
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(endothelin-A receptor antagonist combined with hydralazine improves survival and renal function in hypertensive rats)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

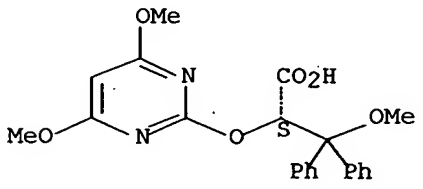
Absolute stereochemistry.



RE.CNT 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 142 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1998:312792 CAPLUS Full-text
DN 129:49423
TI The endothelin-A antagonist LU 135 252 suppresses ischemic ventricular extrasystoles and fibrillation in pigs and prevents hypoxic cellular decoupling
AU Raschack, Manfred; Juchelka, Frieder; Rozek-Schaefer, Gabriela
CS Knoll AG, BASF Pharma, Ludwigshafen, 67008, Germany
SO Journal of Cardiovascular Pharmacology (1998), 31(Suppl. 1, Endothelin V), S145-S148
CODEN: JCPCDT; ISSN: 0160-2446
PB Lippincott-Raven Publishers
DT Journal
LA English
AB The endothelin-A (ETA) antagonist LU 135 252 (1 mg/kg, n = 6 and 3 mg/kg, n = 10) or saline (control, n = 10) was injected i.v. into anesthetized pigs 15 min before occlusion of the last third of the left anterior descending coronary artery (LAD) for up to 90 min. Then, or when ventricular fibrillation occurred, the ischemic mass was determined and amounted to about 13% of ventricular mass in all groups. Heart rate, QT interval, blood pressure, and the left ventricular contractility parameter LV dp/dtmax were not altered by LU in the 15 min pretreatment period. The lower dose of the ETA antagonist had only marginal antiarrhythmic effects. At the 3 mg/kg dose, LU prolonged the time of regular sinus rhythm within the first 20 min of ischemia by 50% (mean ± SEM: 12 ± 2 min in control vs. 18 ± 1 after LU; $p < 0.05$) and reduced the number of ventricular extrasystoles by 87% (54 ± 18 vs. 7 ± 3; $p < 0.05$). The total incidence of ventricular fibrillation (VF) (80% vs. 50%; $p = 0.17$) and also the incidence of late VF (ischemia > 20 min) was reduced by 3 mg/kg LU (78% vs. 38%; $p = 0.12$). In vitro, LU (10-6 mol/L) prevented the hypoxia-induced (N2 gassing) impairment of intercellular coupling, measured as the delay between a direct stimulus and a distal action potential in guinea pig papillary muscles.
IT **171714-84-4**, LU 135252
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(endothelin-A antagonist LU 135252 suppresses ischemic ventricular extrasystoles and fibrillation in pigs and prevents hypoxic cellular decoupling)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

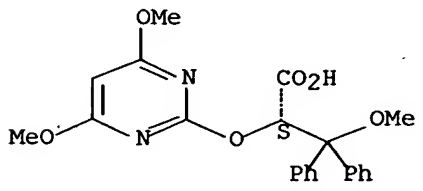
Absolute stereochemistry.



RE.CNT 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 143 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1998:252184 CAPLUS Full-text
DN 129:23134
TI Nephroprotection by an ETA-receptor blocker (LU 135252) in salt-loaded uninephrectomized stroke-prone spontaneously hypertensive rats
AU Orth, Stephan R.; Esslinger, Jan P.; Amann, Kerstin; Schwarz, Ute; Raschack, Manfred; Ritz, Eberhard
CS Dep. Internal Med. Pathol., Ruperto Carola Univ., Heidelberg, D-69115, Germany
SO Hypertension (1998), 31(4), 995-1001
CODEN: HPRTDN; ISSN: 0194-911X
PB Williams & Wilkins
DT Journal
LA English
AB The present study was designed to assess whether the orally active and highly specific endothelin A (ETA) receptor antagonist LU 135252 affects progressive renal dysfunction in a hypertensive rat model of renal damage, ie, the uninephrectomized (UNX) stroke-prone spontaneously hypertensive rat (SHRsp). The animals were examined on a normal salt (0.25%) diet and, to sensitize the kidney to hypertensive injury, also on a high salt (3%) diet. Stereol. methods were used to quantify indexes of glomerulosclerosis, vascular damage, and tubulointerstitial damage. Treatment with LU 135252 (100 mg/kg body weight) did not affect systolic blood pressure (BP) in animals on a normal salt diet during the whole period of the experiment (18 wk) or in salt-loaded animals until week 10; subsequently, BP was slightly but significantly lower in salt-loaded UNX-SHRsp given LU 135252. Between weeks 6 and 12, 40% of the untreated 135252. Indexes of renal damage were more abnormal in salt-loaded UNX-SHRsp compared with UNX-SHRsp on a normal salt diet. Development of glomerulosclerosis and tubulointerstitial and vascular damage in UNX-SHRsp on high salt was completely prevented by LU 135252. The resp. indexes were no long significantly different from those of salt-loaded sham-operated SHRsp controls. In the less severely damaged kidneys of UNX-SHRsp on normal salt, treatment with LU 135252 tended to ameliorate the indexes, but the difference was not statistically significant. The results document a role of the ET system, specifically of ETA receptors, in the development of progressive renal injury in salt-loaded UNX-SHRsp. LU 135252 completely prevented death and renal damage resulting from salt loading.
IT **171714-84-4**, LU 135252
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nephroprotection by an ETA-receptor blocker (LU 135252) in salt-loaded uninephrectomized stroke-prone spontaneously hypertensive rats)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

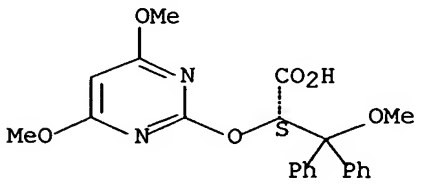
Absolute stereochemistry.



RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 144 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1998:176670 CAPLUS Full-text
DN 128:281349
TI Endothelin-1 and unstable angina: effect of either endothelin ETA or ETB receptor antagonism in a locally injured canine coronary artery
AU Kirchengast, Michael; Hergenroder, Stefan; Schult, Sabine; Munter, Klaus; Rubsamen, Klaus
CS Preclinical Cardiology, Knoll AG, Ludwigshafen, D-67008, Germany
SO European Journal of Pharmacology (1998), 341(2/3), 187-190
CODEN: EJPHAZ; ISSN: 0014-2999
PB Elsevier Science B.V.
DT Journal
LA English
AB The role of endogenous endothelin-1 in variant angina was investigated using two endothelin receptor antagonists: LU 135252 (ETA) and BQ 788 (ETB). Cyclic flow redns. were induced in a coronary artery of mongrel dogs by combining critical stenosis with endothelial injury. One hour after induction of cyclic coronary flow redns. the dogs were randomized to i.v. treatment with either saline, or LU 135252 (10 mg kg-1), or BQ 788 (0.1 mg kg-1). Cyclic coronary flow redns. were monitored for two hours after drug and remained constant in controls as well as after BQ 788. LU 135252 reduced the number of cyclic coronary flow redns. significantly (about 50%) without effects on hemodynamics or hemostasis.
IT **171714-84-4**, LU 135252
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(endothelin ETA or ETB receptor antagonism effects in a locally injured canine coronary artery model of unstable angina)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

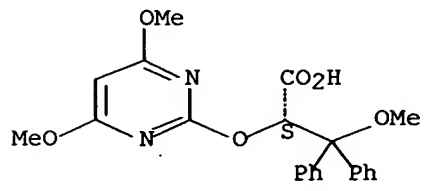
Absolute stereochemistry.



RE.CNT 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 145 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1998:91970 CAPLUS Full-text
DN 128:213006
TI ETA receptor blockade prevents increased tissue endothelin-1, vascular hypertrophy, and endothelial dysfunction in salt-sensitive hypertension
AU Barton, Matthias; D'Uscio, Livius V.; Shaw, Sidney; Meyer, Peter; Moreau, Pierre; Luescher, Thomas F.
CS University Hospital Zurich, Institute of Physiology, University of Zurich, Zurich, CH-8091, Switz.
SO Hypertension (1998), 31(1, Pt. 2), 499-504
CODEN: HPRTDN; ISSN: 0194-911X
PB Williams & Wilkins
DT Journal
LA English
AB Na+ plays an important role in the pathogenesis and therapy of hypertension, a major risk factor for cardiovascular disease. The involvement of endothelin in vascular alterations in salt-induced Dahl hypertension was investigated. Salt-sensitive (DS) and salt-resistant (DR) Dahl rats were treated with a high-Na diet (NaCl 4%) with or without ETA receptor antagonist LU 135252 for 2 mo, and effects of treatments on systolic blood pressure, vascular endothelin-1 (ET-1) protein content, aortic hypertrophy, and vascular reactivity of isolated aortic rings were studied. In DS rats, a high-Na diet increased systolic pressure (190 vs. 152 mm Hg) and aortic ET-1 protein content (4.2-fold) and induced aortic hypertrophy as assessed by tissue weight The high-Na diet markedly reduced NO-mediated endothelium-dependent relaxations in response to acetylcholine (49 vs. 81%) and contractions in response to ET-1 (92 vs. 136% of KCl). ET-1 tissue levels were highly and inversely correlated with endothelium-dependent relaxations and contractions in response to ET. LU 135252 treatment reduced systolic blood pressure only in part (168 vs. 190 mm Hg) but normalized Na+-induced changes of vascular reactivity, tissue ET-1 protein content, and vascular structure. None of these effects were observed in DR rats. Evidently ET-1 acts as a local mediator of vascular dysfunction and aortic hypertrophy in Dahl salt-induced hypertension. ETA receptor antagonism may have therapeutic potential for lowering vascular ET-1 content, improving endothelial function, and preventing structural changes in salt-sensitive hypertension.
IT **171714-84-4**, LU 135252
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ETA receptor blockade prevents increased tissue endothelin-1, vascular hypertrophy, and endothelial dysfunction in salt-sensitive hypertension)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

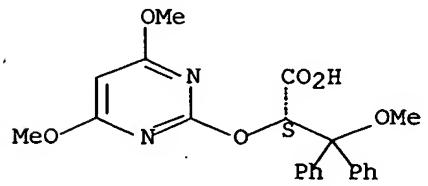
Absolute stereochemistry.



RE.CNT 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 146 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1998:61263 CAPLUS Full-text
DN 128:176413
TI ETA and ETB specific ligands synergistically antagonize endothelin-1 binding to an atypical endothelin receptor in primary rat astrocytes
AU Jensen, Niels; Hasselblatt, Martin; Siren, Anna-Leena; Schilling, Lothar; Schmidt, Martin; Ehrenreich, Hannelore
CS Department of Neurology and Psychiatry, Georg-August-University, Gottingen, Germany
SO Journal of Neurochemistry (1998), 70(2), 473-482
CODEN: JONRA9; ISSN: 0022-3042
PB Lippincott-Raven Publishers
DT Journal
LA English
AB Using a whole-cell binding procedure with long incubations at low temperature and subsequent acid stripping, we have characterized an atypical endothelin (ET) receptor in primary rat cortical astrocyte cultures. We found the following: (a) no competition for 125I-ET-1 binding by the ETA antagonists BQ-123 and LU 135252 or the ETB agonist IRL 1620; (b) weak competition by the ETB antagonist BQ-788 and by the predominant ETB ligand ET-3; (c) potent synergistic competition of ETA and ETB ligands in combination for 125I-ET-1 binding; (d) potent competition of ET-1 with any of the radioligands used, 125I-ET-1, 125I-IRL 1620, and [3H]BQ-123; (e) lack of competition of IRL 1620 and BQ-123 with the resp. other radioligand; (f) shifting of the amount of acid-strippable 125I-ET-1 binding from 20 to 80% by ETB ligands and to 4% by ETA ligands; and (g) as a control, typical ETA and ETB binding characteristics of the RAT-1 fibroblast and the U373MG astrocytoma cell line, resp., under our assay conditions. The unusual binding properties of astrocytic ET receptors described in this study appear to be the result of several binding sites in the receptor for different ET ligands or ligand epitopes.
IT **171714-84-4**, LU 135252
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(ETA and ETB specific ligands synergistically antagonize endothelin-1 binding to atypical endothelin receptor in primary rat astrocytes)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

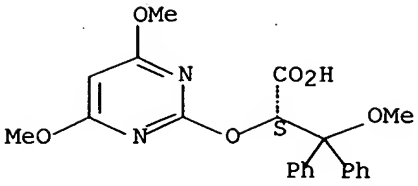
Absolute stereochemistry.



RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 147 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1998:24039 CAPLUS Full-text
DN 128:123591
TI Apoptosis in aorta of deoxycorticosterone acetate-salt hypertensive rats: effect of endothelin receptor antagonism
AU Sharifi, Ali M.; Schiffrin, Ernesto L.
CS MRC Multidisciplinary Research Group on Hypertension, Clinical Research Institute of Montreal, University of Montreal, Montreal, QC, H2W 1R7, Can.
SO Journal of Hypertension (1997), 15(12, Pt. 1), 1441-1448
CODEN: JOHYD3; ISSN: 0263-6352
PB Rapid Science Publishers
DT Journal
LA English
AB Apoptosis or programmed cell death could be greater than normal in various cardiovascular disorders, particularly in the heart. Apoptosis might contribute to remodeling of blood vessels in hypertension and could participate in regulation of vascular hypertrophy/hyperplasia. To investigate apoptosis in deoxycorticosterone acetate (DOCA)-salt hypertension and to determine whether endothelin-1, whose expression is enhanced in these rats, plays a role in apoptosis. We administered two orally active endothelin-A (ETA)-selective receptor antagonist, A-127 722.5 (30 mg/kg per day) and LU 135 252 (50 mg/kg per day), to establish whether antigrowth effects of these ETA antagonists are in part mediated through apoptosis. Apoptosis was evaluated by radiolabeling of 3' OH ends of fragmented DNA, extracted from aortas, using terminal deoxynucleotidyl transferase, to show the presence of internucleosomal DNA splicing as "DNA laddering". Its presence was confirmed by in-situ end-labeling. Systolic blood pressure was slightly but significantly lower in treated than it was in untreated DOCA-salt hypertensive rats by a mean of 26 mmHg ($P < 0.01$) after 4 wk of treatment with A-127 722.5 and by 19 mmHg ($P < 0.01$) in rats treated with LU 135 252. Aortic cross-sectional area (CSA) was significantly greater ($P < 0.001$) in DOCA-salt rats than it was in uninephrectomized controls. This increased CSA was normalized by both ETA antagonists. DOCA-salt rats exhibited a greater degree of apoptosis (evaluated by DNA "laddering") in aorta (353 ± 14 pixels/μg DNA) than did control rats (232 ± 10 pixels/μg DNA, $P < 0.01$). The magnitude of apoptosis was significantly greater ($P < 0.01$) in aorta of endothelin-antagonist-treated than it was in aorta of untreated DOCA-salt hypertensive rats. In-situ end-labeling confirmed that more apoptosis had occurred in the media of aorta from DOCA-salt hypertensive rats and the further increase found after treatment with the ETA antagonists. An increase in apoptosis occurs in aorta of DOCA-salt hypertensive rats, probably as a physiol. counterpart of growth in this hypertensive model. ETA antagonists may act in part by accentuating the apoptosis, thereby inducing a blunting of vascular growth, which could also contribute to their antihypertensive effects.
IT **171714-84-4**, LU 135252
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(endothelin receptor antagonists effects on apoptosis of aorta in deoxycorticosterone acetate-salt hypertensive rats)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

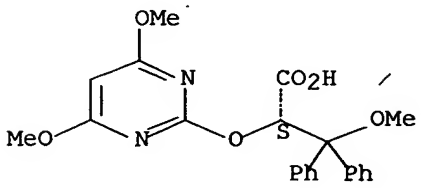
Absolute stereochemistry.



RE.CNT 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 148 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1997:710122 CAPLUS Full-text
DN 127:344772
TI Structure and function of small arteries in salt-induced hypertension. Effects of chronic endothelin-subtype-A-receptor blockade
AU D'Uscio, Livius V.; Barton, Matthias; Shaw, Sidney; Moreau, Pierre; Luscher, Thomas F.
CS Division of Cardiology, Cardiovascular Research, University Hospital, Bern, Switz.
SO Hypertension (Dallas) (1997), 30(4), 905-911
CODEN: HPRTDN; ISSN: 0194-911X
PB American Heart Association
DT Journal
LA English
AB The involvement of endothelin in salt-induced hypertension is unclear. In the Dahl rat model, we studied the effects of a selective endothelin-subtype A (ETA) receptor antagonist, LU135252, on blood pressure, vascular structure, and function. Dahl salt-sensitive and salt-resistant rats were treated for 8 wk with 4% NaCl alone or in combination with LU135252 taken orally (60 mg/kg per day). The geometry and reactivity of basilar and mesenteric arteries were studied in vitro under perfused and pressurized conditions using a video dimension analyzer. Chronic salt administration increased systolic blood pressure by 37 mm Hg and media-lumen ratio of the basilar and mesenteric arteries in salt-sensitive rats. These structural changes were caused by eutrophic remodeling in basilar and hypertrophic remodeling in mesenteric arteries. Endothelium-dependent relaxations to acetylcholine and contractions to endothelin-1 were impaired in mesenteric arteries of salt-sensitive rats on a high NaCl diet. LU135252 prevented part of the increase in systolic blood pressure and structural and functional alterations but increased plasma endothelin 1 levels. LU135252 had no effect on these parameters in salt-resistant rats. These findings suggest that the long-term pressor effect of salt administration is mediated in part by the action of endogenous endothelin acting via ETA receptors. Thus, chronic ETA receptor blockade may be useful therapeutically to lower arterial pressure and prevent endothelial dysfunction and hypertrophic remodeling of resistance arteries in salt-sensitive forms of hypertension.
IT **171714-84-4**, LU 135252
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of chronic endothelin-subtype-A-receptor blockade on structure and function of small arteries in salt-induced hypertension)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

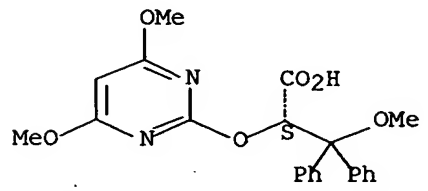
Absolute stereochemistry.



RE.CNT 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 149 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1997:645657 CAPLUS Full-text
DN 127:314563
TI The orally active ETA receptor antagonist (+)-(S)-2-(4,6-dimethoxy-pyrimidin-2-yloxy)-3-methoxy-3,3-diphenyl propionic acid (LU 135252) prevents the development of pulmonary hypertension and endothelial metabolic dysfunction in monocrotaline-treated rats
AU Prie, Stephane; Leung, Tack Ki; Cernacek, Peter; Ryan, James W.; Dupuis, Jocelyn
CS Department of Medicine, Royal Victoria Hospital, Montreal, QC, Can.
SO Journal of Pharmacology and Experimental Therapeutics (1997), 282(3), 1312-1318
CODEN: JPETAB; ISSN: 0022-3565
PB Williams & Wilkins
DT Journal
LA English
AB Pulmonary hypertension is associated with endothelial dysfunction that may mediate or contribute to the disease process; among those abnormalities is an increase in circulating endothelin-1 levels. We investigated the effect of the orally active endothelin A receptor antagonist LU 135252 (LU) on the development of monocrotaline (MCT)-induced pulmonary hypertension and endothelial metabolic dysfunction. Rats were assigned to four groups by receiving a single dose of MCT or saline, followed by once-daily gavage with LU (50 mg/kg) or saline for 3 wk. Plasma immunoreactive endothelin-1 levels doubled after MCT and were unaffected by LU therapy. The MCT-induced increase in right ventricular systolic pressure (72.5 mmHg) and hypertrophy (right ventricle/[left ventricle plus septum weight]; 0.58) were reduced by LU to 42.7 mmHg and 0.42, resp. LU, however, did not modify MCT-induced pulmonary artery medial hypertrophy. Pulmonary vascular endothelial metabolic activity was evaluated in isolated lungs by measuring endothelium-bound angiotensin-converting enzyme activity using a synthetic angiotensin-converting enzyme substrate, 3H-benzoyl-phenylalanyl-glycyl-proline. MCT reduced fractional 3H-benzoyl-phenylalanyl-glycyl-proline hydrolysis (0.488) which was normalized by LU therapy (0.563). LU treatment alone had no significant effect on any of these parameters. We conclude that the endothelin A antagonist LU reduces MCT-induced pulmonary hypertension and right ventricular hypertrophy and restores endothelial metabolic function. These results support the development of endothelin antagonists for the treatment of pulmonary hypertension and associated endothelial metabolic abnormalities.
IT **171714-84-4**, LU 135252
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ETA receptor antagonist LU 135252 prevents development of pulmonary hypertension and endothelial metabolic dysfunction in monocrotaline-treated rats)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

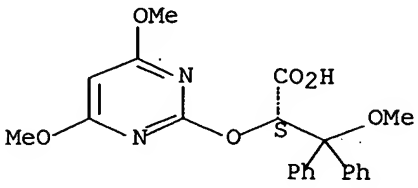


RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD

L11 ANSWER 150 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1997:459109 CAPLUS Full-text
DN 127:171298
TI Effect of chronic ETA-selective endothelin receptor antagonism on blood pressure in experimental and genetic hypertension in rats
AU Schiffrin, Ernesto L.; Turgeon, Andre; Deng, Li Y.
CS MRC Multidisciplinary Research Group on Hypertension, Clinical Research Institute of Montreal, University of Montreal, Montreal, QC, H2W 1R7, Can.
SO British Journal of Pharmacology (1997), 121(5), 935-940
CODEN: BJPCBM; ISSN: 0007-1188
PB Stockton
DT Journal
LA English
AB Chronic treatment with a combined ETA/ETB endothelin receptor antagonist has been shown to reduce blood pressure in exptl. rat models of hypertension in which endothelin-1 gene overexpression occurs in the walls of blood vessels, particularly small, resistance-sized arteries, but not in those genetic or exptl. models of hypertension in which there is no overexpression of vascular endothelin-1. Failure of some exptl. models of hypertension to respond to treatment with the combined ETA/ETB endothelin antagonist may be due in part to blockade of vasorelaxant endothelial ETB receptors which could in theory reduce the efficacy of endothelin antagonism. In this study the orally active ETA-selective endothelin antagonists A-127722.5 and LU 135252 were used in chronic expts. on deoxycorticosterone acetate (DOCA)-salt hypertensive rats (which overexpress vascular endothelin-1 and respond with blood pressure lowering to combined ETA/ETB endothelin receptor antagonism), on spontaneously hypertensive rats (SHR) (which do not overexpress vascular endothelin-1 and do not respond with blood pressure lowering to the combined ETA/ETB receptor antagonist), and in 1-kidney 1 clip Goldblatt (1-K 1C) hypertensive rats (which present mild overexpression of vascular endothelin-1 but do not respond with blood pressure lowering to the combined ETA/ETB receptor antagonist). Addnl., it has been suggested that interruption of the renin-angiotensin system may sensitize responses to endothelin antagonism. Accordingly, SHR were treated with an angiotensin converting enzyme inhibitor, cilazapril, in addition to the ETA receptor antagonist. Blood pressure of DOCA-salt hypertensive rats was lowered by a mean of 24 and of 27 mm Hg ($P<0.01$) by A-127722.5 after 4 wk of treatment, when given orally at two different doses (10 and 30 mg kg-1 day-1), and by 18 mm Hg by LU 135252 50 mg kg-1 day-1. SHR treated with A-127722.5 for 8 wk starting at 12 wk of age exhibited the same progressive rise in blood pressure as untreated SHR. Addition of cilazapril resulted in similar reduction of blood pressure in A-127722.5-treated and untreated SHR. Treatment of 1-K 1C hypertensive rats with the dose of LU 135252 which lowered blood pressure in DOCA-salt hypertensive rats did not cause any reduction in blood pressure relative to untreated rats. These results demonstrate that treatment with either dose of the selective ETA receptor antagonists A-127722.5 or LU 135252 caused redns. in blood pressure similar to those obtained for a combined ETA/ETB endothelin antagonist. Blood pressure was lowered only in hypertensive rats known to overexpress vascular endothelin-1 (DOCA-salt hypertensive rats) but not in those which do not (SHR) or only have mild vascular overexpression of endothelin-1 gene (1-K 1C hypertensive rats). Reduction in activity of the renin-angiotensin system in SHR did not sensitize blood pressure to potential hypotensive effects of an ETA-selective receptor antagonist.
IT **171714-84-4**, LU 135252
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effect of chronic ETA-selective endothelin receptor antagonism on blood pressure in exptl. and genetic hypertension in rats)
RN 171714-84-4 CAPLUS

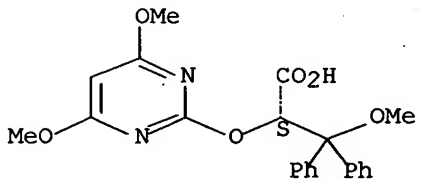
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



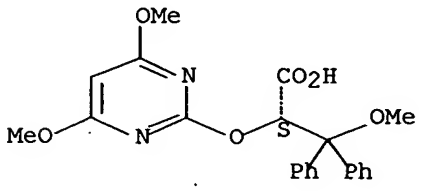
L11 ANSWER 151 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1997:402671 CAPLUS Full-text
DN 127:157209
TI Endothelin-1 mediates the development of severe acute pancreatitis
AU Foitzik, Thomas; Faulhaber, J.; Hotz, H. G.; Kirchengast, M.; Buhr, H. J.
CS Abteilung Allgemein-, Gefass- Thoraxchirurgie, Klinikum Benjamin Franklin, Berlin, D-12200, Germany
SO Chirurgisches Forum fuer Experimentelle und Klinische Forschung (1997) 749-753
CODEN: CFEKA7; ISSN: 0303-6227
PB Springer
DT Journal
LA German
AB In edematous pancreatitis of rats, endothelin-1 (ET-1) decreased pancreatic capillary blood flow and caused development of acinar cell necrosis. Transgenic rats with ET-1 receptor overexpression developed more severe disease, while prophylactic administration of the selective ET-1 receptor antagonist, LU 135252, ameliorated disease severity. After manifestation of necrotizing pancreatitis, ET-1 receptor blockade enhanced decreased pancreatic capillary blood flow and decreased mortality although the development of acinar cell necrosis was not diminished. Improved survival was associated with less ascites and decreased hematocrit indicating decreased fluid loss into the 3rd space and suggesting that the antagonist counteracted an ET-1-induced increase in vascular permeability.
IT **171714-84-4**, LU 135252
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(endothelin-1 mediates the development of acute pancreatitis)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



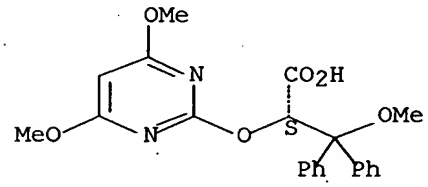
L11 ANSWER 152 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1997:157448 CAPLUS Full-text
DN 126:195755
TI Effects of chronic ETA-receptor blockade in angiotensin II-induced hypertension
AU D'uscio, Livius V.; Moreau, Pierre; Shaw, Sidney; Takase, Hiroyuki; Barton, Matthias; Luscher, Thomas F.
CS Division of Cardiology, Cardiovascular Research, University Hospital, Bern, Switz.
SO Hypertension (Dallas) (1997), 29(1, Pt. 2), 435-441
CODEN: HPRTDN; ISSN: 0194-911X
PB American Heart Association
DT Journal
LA English
AB Angiotensin II, a constrictor and mitogen of vascular smooth muscle cells, affects the release of endothelium-derived factors such as nitric oxide or endothelin-1. This study investigated the influence of endothelin-1, using the selective endothelin A receptor antagonist LU 135252, on blood pressure and endothelial function in angiotensin II-induced hypertension in the rat. Two weeks of angiotensin II administration (200 ng/kg per min) increased systolic blood pressure (35 mm Hg; tail-cuff method) compared with placebo. LU 135252 alone did not affect systolic pressure but lowered the angiotensin II-induced pressure increase. In isolated aortic rings, endothelium-dependent relaxations to acetylcholine were reduced in the angiotensin II group (vs. placebo) and improved by concomitant chronic LU 135252 treatment (vs. angiotensin II). Blood pressure elevation strongly correlated with impaired endothelium-dependent relaxations to acetylcholine. LU 135252 did not affect endothelium-independent relaxations to sodium nitroprusside, which were diminished after angiotensin II treatment. In quiescent rings, chronic angiotensin II administration enhanced endothelium-dependent contractions to acetylcholine, which were reduced by LU 135252. Impaired contractions to endothelin-1 and norepinephrine in the angiotensin II group were normalized after treatment with LU 135252. Thus, chronic therapy with LU 135252 partially prevents angiotensin II-induced hypertension and the alterations of the endothelial function observed in this exptl. model.
IT **171714-84-4**, LU 135252
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of chronic ETA-receptor blockade in angiotensin II-induced hypertension)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L11 ANSWER 153 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1996:625015 CAPLUS Full-text
DN 125:316842
TI Oral treatment with an ETA-receptor antagonist inhibits neointima formation induced by endothelial injury
AU Muenter, K.; Hergenroeder, S.; Unger, L.; Kirchengast, M.
CS Knoll A.-G., Ludwigshafen, D-67008, Germany
SO Pharmaceutical and Pharmacological Letters (1996), 6(2), 90-92
CODEN: PPLEE3; ISSN: 0939-9488
PB Medpharm Scientific Publishers
DT Journal
LA English
AB Rats were orally treated with the selective ETA-receptor antagonist LU 135252 from 3 days before until 13 days after ballooning of the left carotid artery. Development of stenosis was assessed histol. 2 wk after balloon injury. The neointima/media ratio was dose-dependent and reduced from 1.60 (control) to 1.38 (20 mg/kg/d), (50 mg/kg/d) and 1.20 (100 mg/kg/d). Thus, oral treatment with a selective ETA-receptor antagonist reduced the proliferative response to endothelial denudation in the rat.
IT **171714-84-4**, LU 135252
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(ETA-receptor antagonist LU 135252 inhibits neointima formation induced by endothelial injury)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L11 ANSWER 154 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1996:401554 CAPLUS Full-text
DN 125:58534
TI Preparation of pyrimidine- and triazine-derivative endothelin receptor antagonists
IN Riechers, Hartmut; Klinge, Dagmar; Amberg, Wilhelm; Kling, Andreas; Mueller, Stefan; Baumann, Ernst; Rheinheimer, Joachim; Vogelbacher, Uwe Josef; Wernet, Wolfgang; et al.
PA BASF A.-G., Germany
SO Ger. Offen., 28 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 1

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PI	DE 19533023	A1	19960418	DE 1995-19533023	19950907
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	CN 1513844	A	20040721	CN 2004-10002783	19951007
	AT 277911	E	20041015	AT 2001-103889	19951007
	CZ 294603	B6	20050216	CZ 1997-1132	19951007
	ES 2226996	T3	20050401	ES 2001-103889	19951007
	IL 115560	A1	20030212	IL 1995-115560	19951011
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	US 5932730	A	19990803	US 1997-809699	19970327
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	US 2004092742	A1	20040513	US 2003-602275	20030624
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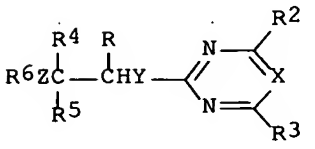
	DE 1995-19533023	A	19950907		
	EP 1995-935916	A3	19951007		

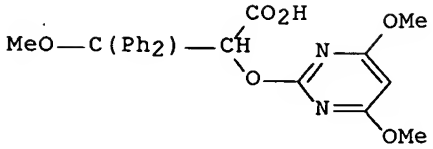
	WO 1995-EP3963	W	19951007
	US 1998-184152	A3	19981102
	US 1999-309770	A3	19990511
	US 2000-748184	A1	20001227

OS MARPAT 125:58534

GI



I



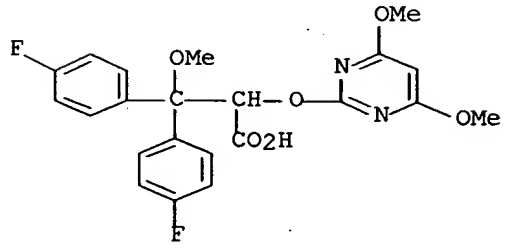
II

AB The title compds. [I; R = CHO, tetrazolyl, CN, CO2H, groups cleavable to CO2H; R2 = (un)substituted NH2, halogen, (un)substituted alkyl, etc.; R3 = H, OH, (un)substituted NH2, halogen, (un)substituted alkyl, etc.; R4, R5 = (un)substituted Ph or naphthyl; R6 = H, alkyl, alkenyl, alkynyl, alkylcarbonyl, (un)substituted Ph, etc.; X = N, (un)substituted CH; Y = direct bond, S, O; Z = S, O, SO, SO2, direct bond], useful as endothelin receptor antagonists, are prepared Thus, pyrimidine derivative II, m.p. 167°, demonstrated a Ki ETA of 6 nM.

IT **177036-81-6P 177036-86-1P 177036-87-2P**
178306-45-1P 178306-46-2P 178306-57-5P
178306-66-6P 178306-67-7P 178306-69-9P
178306-83-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of pyrimidine- and triazine-derivative endothelin receptor antagonists)

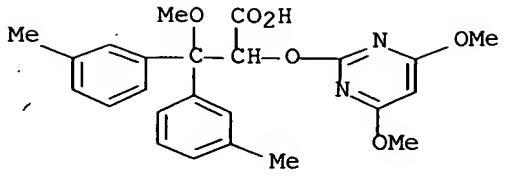
RN 177036-81-6 CAPLUS

CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-4-fluoro-β-(4-fluorophenyl)-β-methoxy- (9CI) (CA INDEX NAME)



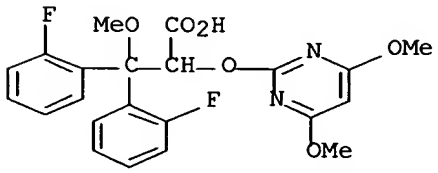
RN 177036-86-1 CAPLUS

CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-3-methyl-β-(3-methylphenyl)- (9CI) (CA INDEX NAME)



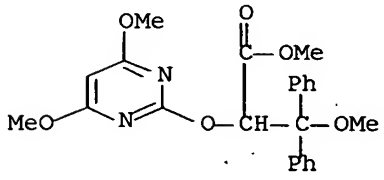
RN 177036-87-2 CAPLUS

CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-2-fluoro-β-(2-fluorophenyl)-β-methoxy- (9CI) (CA INDEX NAME)



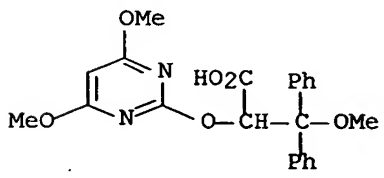
RN 178306-45-1 CAPLUS

CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, methyl ester (9CI) (CA INDEX NAME)



RN 178306-46-2 CAPLUS

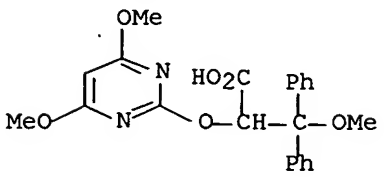
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl- (9CI) (CA INDEX NAME)



RN 178306-57-5 CAPLUS

CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-

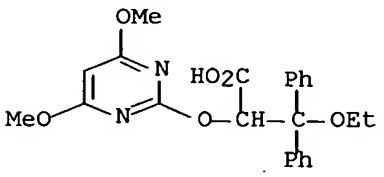
methoxy-β-phenyl-, sodium salt (9CI) (CA INDEX NAME)



● Na

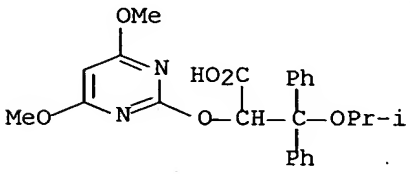
RN 178306-66-6 CAPLUS

CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-ethoxy-β-phenyl- (9CI) (CA INDEX NAME)



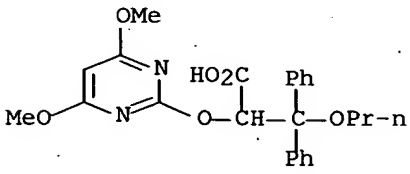
RN 178306-67-7 CAPLUS

CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-(1-methylethoxy)-β-phenyl- (9CI) (CA INDEX NAME)



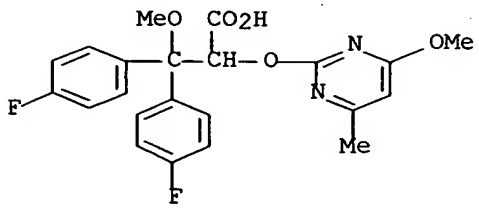
RN 178306-69-9 CAPLUS

CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-phenyl-β-propoxy- (9CI) (CA INDEX NAME)



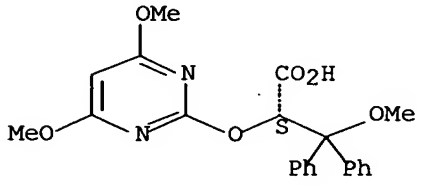
RN 178306-83-7 CAPLUS

CN Benzenepropanoic acid, 4-fluoro-β-(4-fluorophenyl)-β-methoxy-α-[(4-methoxy-6-methyl-2-pyrimidinyl)oxy]- (9CI) (CA INDEX NAME)

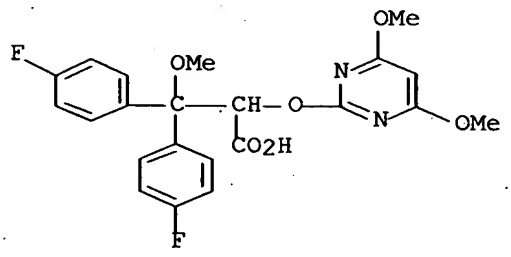


L11 ANSWER 155 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1996:271791 CAPLUS Full-text
DN 125:328
TI Discovery and Optimization of a Novel Class of Orally Active Nonpeptidic Endothelin-A Receptor Antagonists
AU Riechers, Hartmut; Albrecht, Hans-Peter; Amberg, Willi; Baumann, Ernst; Bernard, Harald; Boehm, Hans-Joachim; Klinge, Dagmar; Kling, Andreas; Mueller, Stefan; et al.
CS Hauptlaboratorium, BASF AG, Ludwigshafen, 67056, Germany
SO Journal of Medicinal Chemistry (1996), 39(11), 2123-8
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
OS CASREACT 125:328
AB A novel class of endothelin-A receptor ligands was discovered by high-throughput screening. Lead structure optimization led to highly potent antagonists which can be synthesized in a short sequence. The compds. are endothelin-A-selective, are orally available, and show a long duration of action.
IT **171714-84-4P**, LU 127043 **177036-81-6P**
177036-82-7P 177036-83-8P 177036-84-9P
177036-85-0P 177036-86-1P 177036-87-2P
177036-88-3P 177036-89-4P 177036-93-0P
177036-94-1P 177036-98-5P 177036-99-6P
177037-00-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of a novel class of orally active nonpeptidic endothelin-a receptor antagonists)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

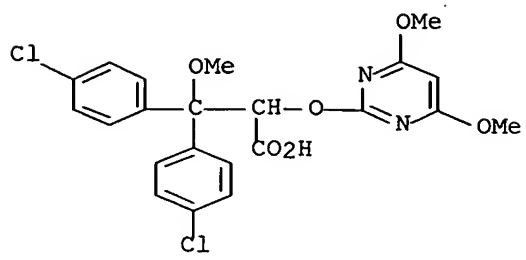


RN 177036-81-6 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-4-fluoro-β-(4-fluorophenyl)-β-methoxy- (9CI) (CA INDEX NAME)



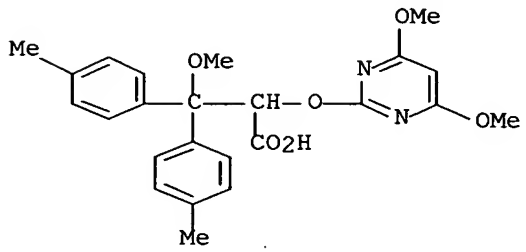
RN 177036-82-7 CAPLUS
CN Benzenepropanoic acid, 4-chloro-β-(4-chlorophenyl)-α-[(4,6-

dimethoxy-2-pyrimidinyl)oxy]-β-methoxy- (9CI) (CA INDEX NAME)



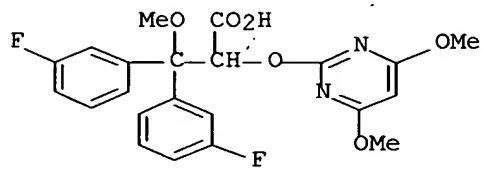
RN 177036-83-8 CAPLUS

CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-4-methyl-β-(4-methylphenyl)- (9CI) (CA INDEX NAME)



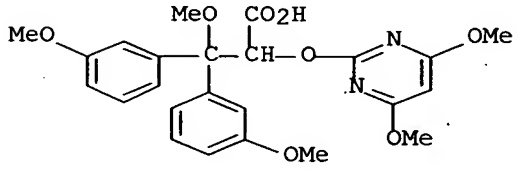
RN 177036-84-9 CAPLUS

CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-3-fluoro-β-(3-fluorophenyl)-β-methoxy- (9CI) (CA INDEX NAME)



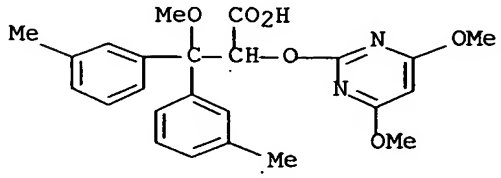
RN 177036-85-0 CAPLUS

CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β,3-dimethoxy-β-(3-methoxyphenyl)- (9CI) (CA INDEX NAME)



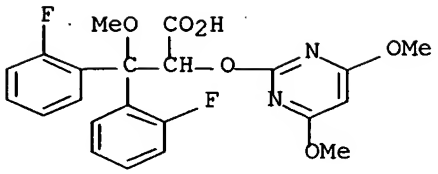
RN 177036-86-1 CAPLUS

CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-3-methyl-β-(3-methylphenyl)- (9CI) (CA INDEX NAME)



RN 177036-87-2 CAPLUS

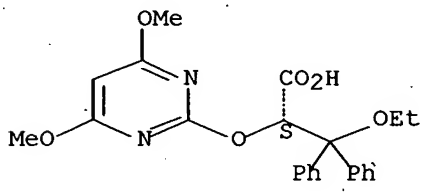
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-2-fluoro-β-(2-fluorophenyl)-β-methoxy- (9CI) (CA INDEX NAME)



RN 177036-88-3 CAPLUS

CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-ethoxy-β-phenyl-, (S)- (9CI) (CA INDEX NAME)

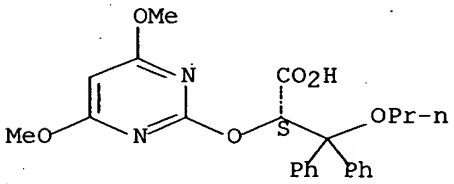
Absolute stereochemistry.



RN 177036-89-4 CAPLUS

CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-phenyl-β-propoxy-, (S)- (9CI) (CA INDEX NAME)

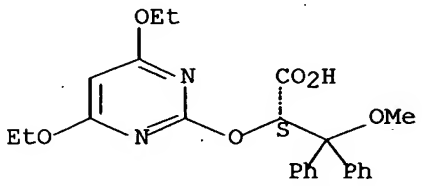
Absolute stereochemistry.



RN 177036-93-0 CAPLUS

CN Benzenepropanoic acid, α-[(4,6-diethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (S)- (9CI) (CA INDEX NAME)

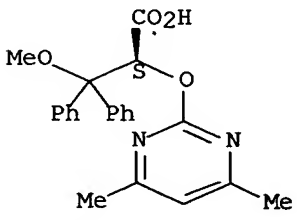
Absolute stereochemistry.



RN 177036-94-1 CAPLUS

CN Benzenepropanoic acid, α-[(4,6-dimethyl-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

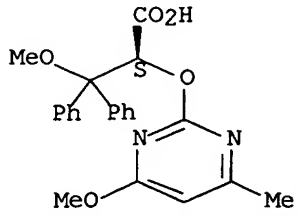
Absolute stereochemistry.



RN 177036-98-5 CAPLUS

CN Benzenepropanoic acid, β-methoxy-α-[(4-methoxy-6-methyl-2-pyrimidinyl)oxy]-β-phenyl-, (S)- (9CI) (CA INDEX NAME)

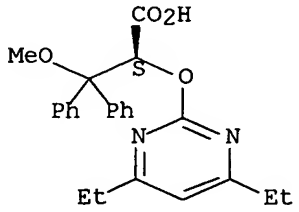
Absolute stereochemistry.



RN 177036-99-6 CAPLUS

CN Benzenepropanoic acid, α-[(4,6-diethyl-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (S)- (9CI) (CA INDEX NAME)

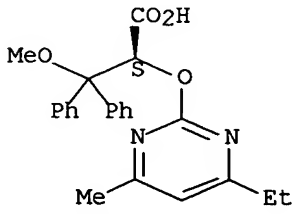
Absolute stereochemistry.



RN 177037-00-2 CAPLUS

CN Benzenepropanoic acid, α-[(4-ethyl-6-methyl-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **177036-79-2P**

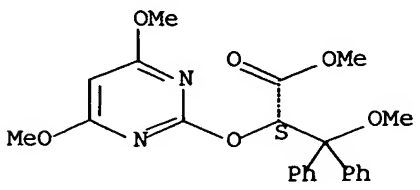
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of a novel class of orally active nonpeptidic endothelin-a receptor antagonists)

RN 177036-79-2 CAPLUS

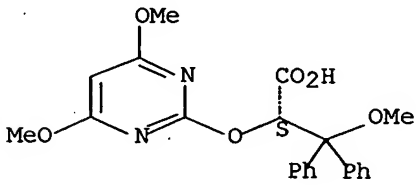
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, methyl ester, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

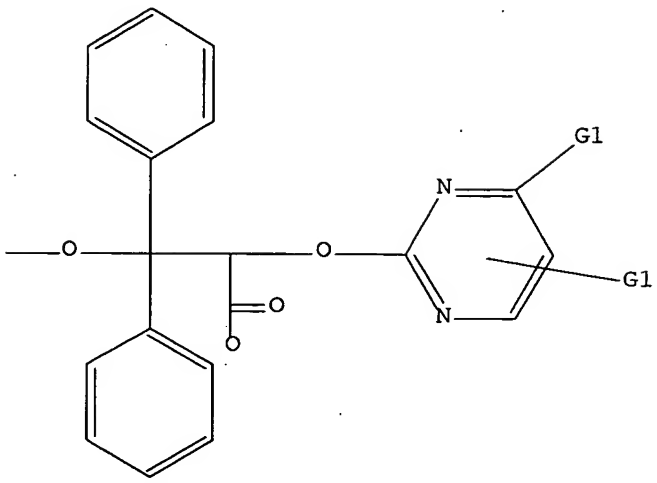


L11 ANSWER 156 OF 156 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1995:966284 CAPLUS Full-text
DN 124:22417
TI Receptor selectivity of endothelin antagonists and prevention of vasoconstriction and endothelin-induced sudden death
AU Raschack, Manfred; Unger, Liliane; Riechers, Hartmut; Klinge, Dagmar
CS Knoll AG, Ludwigshafen, Germany
SO Journal of Cardiovascular Pharmacology (1995), 26(Suppl. 3), S397-S399
CODEN: JCPCDT; ISSN: 0160-2446
PB Lippincott-Raven
DT Journal
LA English
AB The new endothelin (ET) receptor antagonist LU 127043 shows higher ETA affinity than BQ 123, Ro 46 2005, and BMS 182874, with a Ki of 6 nmol/L vs. 19, 28, and 57 nmol/L. ETA/ETB selectivity of LU 127043 of about 160 is comparable to that of BQ 123 (200) and is much greater than that of Ro 46-2005 (0.93) and SB 209670 (0.74). In rabbit aortic segments, LU 127043 showed Et antagonistic potency similar to that of BQ 123 and BMS 182874 (pA2 7.34 vs. 7.36 and 7.09), whereas SB 209670 is more potent (9.80). In rats, LU 127043 completely prevents the ET-1-induced sudden death due to coronary constriction, as indicated by a pronounced T-wave increase. With i.v. pretreatment, LU 127043 is as selective as SB 209670, whereas it is three times more active using 4 h oral pretreatment. Even 8 h after oral administration, LU 127043, in contrast to SB 209670, provides dose-dependent protection. Hence, LU 127043 is an example of a selective ETA antagonist with high oral availability and long duration of action. Because the in vivo efficacy of other high affinity ET antagonists is relatively low, further optimization for therapeutic use should concentrate on pharmacokinetic properties.
IT **171714-84-4**, LU 127043
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(receptor selectivity of endothelin antagonists and prevention of vasoconstriction and endothelin-induced sudden death)
RN 171714-84-4 CAPLUS
CN Benzenepropanoic acid, α-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-β-methoxy-β-phenyl-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



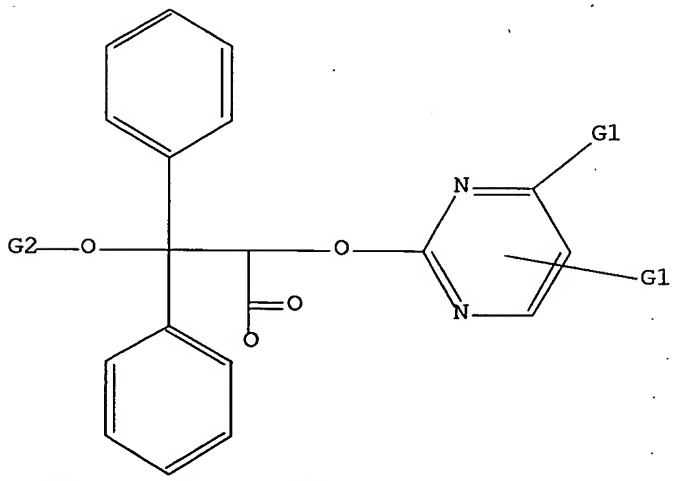
=> d l2; d l8; d his; log y
L2 HAS NO ANSWERS
L1 STR



G1 Me,Et,n-Pr,i-Pr,MeO,EtO,n-PrO,i-PrO

Structure attributes must be viewed using STN Express query preparation.
L2 QUE ABB=ON PLU=ON L1

L8 HAS NO ANSWERS
L7 STR



G1 Me,Et,n-Pr,i-Pr,MeO,EtO,n-PrO,i-PrO
G2 Me,Et,n-Pr,i-Pr

Structure attributes must be viewed using STN Express query preparation.
L8 QUE ABB=ON PLU=ON L7

(FILE 'HOME' ENTERED AT 18:30:33 ON 28 MAR 2006)

FILE 'REGISTRY' ENTERED AT 18:30:40 ON 28 MAR 2006
L1 STRUCTURE UPLOADED
L2 QUE L1
L3 5 S L2
L4 184 S L2 FUL

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     FILE 'CAPLUS' ENTERED AT 18:31:44 ON 28 MAR 2006
L5           172 S L4
L6           ANALYZE L5 1-172 RN :    4044 TERMS

     FILE 'REGISTRY' ENTERED AT 18:32:58 ON 28 MAR 2006
L7                STRUCTURE UPLOADED
L8                QUE L7
L9             0 S L8 SAM SUB=L4
L10           40 S L8 FUL SUB=L4

     FILE 'CAPLUS' ENTERED AT 18:34:40 ON 28 MAR 2006
L11          156 S L10


COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                   798.54    1018.62

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                  -117.00    -117.00

STN INTERNATIONAL LOGOFF AT 18:36:32 ON 28 MAR 2006
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